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The Effects of Cannabinoids on Sleep

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Abstract

The use of cannabis products to help with sleep and various other medical conditions by the public has increased significantly in recent years. Withdrawal from cannabinoids can lead to sleep disturbance. Here, we describe a patient who developed significant insomnia leading to worsening anxiety, mood, and suicidal ideation in the setting of medical cannabis withdrawal, prompting presentation to the Emergency Department and inpatient admission. There is a limited evidence base for the use of cannabis products for sleep. We provide a comprehensive review evaluating the literature on the use of cannabis products on sleep, including an overview of cannabis and related psychoactive compounds, the current state of the law as it pertains to the prescribing and use of these substances, and potential side effects and drug interactions. We specifically discuss the impact of cannabis products on normal sleep and circadian sleep-wake rhythms, insomnia, excessive daytime sleepiness, sleep apnea, parasomnias, and restless legs syndrome. We also describe the effects of cannabis withdrawal on sleep and how this increases relapse to cannabis use. Most of the studies are observational but the few published randomized controlled trials are reviewed. Our comprehensive review of the effects of cannabis products on normal sleep and sleep disorders, relevant to primary care providers and other clinicians evaluating and treating patients who use these types of products, shows that cannabis products have minimal to no effects on sleep disorders and may have deleterious effects in some individuals. Further research examining the differential impact of the various types of cannabinoids that are currently available on each of these sleep disorders is required.

Keywords

cannabis, cannabidiol, sleep, insomnia, sleepiness, sleep apnea, restless legs syndrome, rapid eye movement sleep behavior disorder, treatment

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Case Report

A 24-year-old married, employed, male presented to the Emergency Department (ED) with new-onset suicidal ideation in the context of worsening depression, anxiety, and significant sleep disturbance. His past medical history was significant for attention deficit hyperactivity disorder (ADHD) and posttraumatic stress disorder (PTSD). He was not on any psychotropic medications. He described using medical cannabis which he had obtained from a qualified cannabis dispensary after meeting with an independent provider who certified that he met the qualifying conditions to treat his PTSD symptoms. These symptoms included insomnia, nightmares, and anxiety for over 3 months prior to obtaining medical cannabis. The symptoms had improved with the use of medical cannabis; however, due to the significant expense associated with obtaining medical cannabis, he discontinued its use 2 days prior to his presentation to the ED.

In the first 2 days of discontinuation of medical cannabis, the patient started noticing difficulties with sleep initiation and maintenance, which in turn adversely impacted his mood and anxiety symptoms. He then started experiencing suicidal thoughts and presented to the ED. He was admitted to a specialized mood disorder unit and began treatment with paroxetine. Cognitive behavioral therapy was utilized to address both anxiety and insomnia-related symptoms, with good benefit. His suicidal ideation resolved, and he

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was discharged after 10 days with outpatient follow-up for ongoing therapy and medication management.

Introduction

The use of cannabis products to help with insomnia and other sleep disorders is increasing while evidence supporting their use is limited. Further, withdrawal from cannabis is associated with significant sleep-related symptoms and these sleep disturbances increase the risk of relapse to cannabis use. There are a few older reviews of studies assessing the effects of cannabis products on sleep.[1-11] The objective of the current comprehensive review was to update previous reviews and describe the current literature evaluating the effects of cannabis products on normal sleep and sleep disorders, both during active use as well as during withdrawal. We aimed to discuss the effects of cannabis products on circadian sleep-wake rhythms as well as the evidence for their use in various sleep disorders.

For this comprehensive narrative review, a literature search was performed in Ovid Medline, Embase and Scopus using search terms "cannabis" and "sleep" from January 1, 1960 to July 1, 2021 for all English articles of any study design. A total 818 abstracts were reviewed by authors BK and MPM. Articles published in medical journals but not book chapters were reviewed. Studies of adult human subjects examining the effects of cannabis products on sleep included in this review are summarized in Table 1 (n = 20); review articles and editorials are excluded from this list. No funding was received for this work.

First, we provide an overview of cannabis and psychoactive compounds, the current state of the law as it pertains to the use of these compounds, and potential side effects and drug interactions. We then discuss the effects of cannabis on normal sleep, circadian sleep-wake rhythms, effects on sleep during withdrawal, and conversely, the effects of poor sleep on relapse to cannabis use. Finally, we discuss the impact of cannabis products on sleep-related symptoms and disorders, specifically, insomnia, excessive daytime sleepiness, sleep apnea, parasomnias such as nightmares and rapid eye movement behavior disorder (RBD), and restless legs syndrome (RLS).

Discussion

Overview of Cannabis and Related Products

Cannabis and psychoactive compounds. Cannabinol was the first compound to be extracted from the cannabis plant. In the 1960s, an Israeli researcher Professor Raphael Meacholeum isolated both cannabidiol (CBD) and Δ9-tetrahydrocannabidiol (THC) and demonstrated that THC was the psychoactive compound. There are over 500 different compounds in the cannabis plant. Phytocannabinoids account for over a hundred of these and include Δ9-THC, CBD, and cannabinol. The remainder are non-cannabinoids and include terpenes, phenolic compounds, and alkaloids.

Current state of the law. As of July 2021, recreational cannabis use has been legalized in 18 states in the United States (US) and the District of Columbia. Additionally, the use of medical cannabis is allowed and/or cannabis has been decriminalized in 37 states.

Δ9-THC is classified as a Food and Drug Administration (FDA) schedule I drug in the US. The Hemp Farming Act of 2018 bill legalized industrial hemp that contains a Δ9-THC concentration of less than 0.3% by removing it from schedule I of the Controlled Substances Act. However, CBD derived from hemp plants is not approved by the FDA for use in any medicinal or food and drink products. According to the Drug Enforcement Agency (DEA), CBD that is derived from cannabis plants with more than 0.3% THC is considered illegal. Furthermore, the DEA states that CBD products approved by the FDA and containing a THC level of less than 0.1% would be classified as a schedule V substance; currently Epidiolex™ (FDA-approved prescription CBD) is the only drug that meets these criteria.

Despite the current legal climate, numerous private companies have started manufacturing and marketing CBD and other cannabis products to the public claiming health benefits. The FDA has tested many products claiming to contain CBD and found that they do not contain the stated level of CBD. The FDA has issued several warnings to firms that market these drugs.[12] The FDA also cautions consumers about purchasing these products and states that these products are not approved for the diagnosis, prevention, or treatment of disease. Notably, once the use of marijuana was legalized in the states of Colorado, Oregon, and Nevada in the US and recreational marijuana sales began, medical marijuana patient counts decreased substantially.[13]

Potential side effects of cannabis use. Marijuana use is associated with multiple adverse health and public safety effects.[14] This has been demonstrated with both early use, beginning in adolescence, as well as long-term or heavy use.[15] These effects include increased risk of addiction to marijuana and other substances, motor vehicle accidents, cardiovascular complications in otherwise young and healthy patients, chronic bronchitis, and decreased lifetime achievement.[16-18] Additionally, the use of marijuana can lead to the use of other drugs, abnormal brain development, schizophrenia, depression, and anxiety. A low risk of lung cancer in addition to other cancers has also been associated with its use.[19]

Drug interactions with cannabinoids. There are several potential drug interactions of cannabinoids that are relevant to clinicians; Δ9-THC is a CYP1A2 inducer and can result in

Table 1. Summary of Studies Examining the Impact of Cannabis Products on Normal Sleep and Sleep Disorders.

Study	Design and population	Main results	Conclusions and limitations
1. Levin et al[32]	Study assessing the relationship between cannabis withdrawal and relapse to use. Convenience sample (N = 495) who made a quit attempt in a non-controlled environment and who completed a 175-item MJ Quit Questionnaire.	42.5% had experienced a lifetime withdrawal syndrome; 70.5% endorsed using cannabis in response to withdrawal symptoms, most of which were moderate or greater in intensity. Number of withdrawal symptoms correlated with greater frequency and amount of cannabis use, although alcohol (41%) and tobacco (48%) were used more frequently than cannabis (33%). A total of 65% of subjects reported that sleep disturbance during withdrawal contributed to at least 1 prior episode of relapse.	Cannabis withdrawal could serve as a treatment target in cannabis users. Only subjective sleep symptoms were assessed.
2. Bolla et al[33]	Study examining differences in PSG measures on 2 consecutive nights between recently abstinent heavy MJ users (n = 17) and matched drug-free controls (n = 14), 18-30 yo men and women.	MJ users had lower TST, SWS on both nights and lower sleep efficiency, longer SOL and shorter REM latency on night 2 compared to controls.	MJ users did not show improvements in sleep after an adaptation night. The extent to which these differences were present prior to abstinence was not known.
3. Bolla et al[36]	Study characterizing PSG findings during acute abstinence (n = 18) from heavy MJ use in an inpatient unit on nights 1, 2, 7, 8, and 13 after cessation.	TST, REM sleep, SE declined while WASO and PLMs increased across abstinence. Quantity and duration of MJ use correlated with number of PLMs.	Treatment of sleep disturbance could be a treatment target in cannabis users. The number of subjects was small.
4. Feinberg et al[35]	Study assessing EEG and eye movements in experienced MJ users under placebo and THC conditions (N = 7).	THC decreased the number of REMs and duration of REM sleep, while withdrawal led to increase in both these measures. Stage 4 sleep decreased during the first withdrawal night.	Early study of small sample size evaluating the effects of THC use and withdrawal on sleep stages.
5. Cousens and DiMascio[39]	Experimental study assessing the effects of 3 doses of THC on sleep.	THC at various doses decreased SOL but caused a "hangover effect" the next morning and resulted in temporal disorganization.	Early study assessing the effects of THC as a hypnotic.
6. Shannon et al[40]	Retrospective study (N = 72) in a psychiatric clinic assessing effects of CBD as an adjunctive treatment for sleep and/or anxiety complaints, using validated questionnaires at baseline and monthly after initiation of treatment.	Anxiety was present in 47 and sleep complaints in 25 subjects. Anxiety decreased in 79% and remained low throughout. Sleep improved in the first month in 67% and worsened in 25%; at 2 months, 56% reported improvement and 27% reported worsening sleep.	CBD may have anxiolytic effects but effects on sleep complaints are variable. Only subjective measures of sleep were assessed.
7. Sznitman et al[41]	Study assessing the effects of MC on sleep in patients (N = 128) with chronic pain over the age of 50 years, N = 66 users and n = 62 non-users.	After adjusting for confounders, MC use was associated with less problems waking up. There were no differences between the groups in problems falling asleep or early morning awakenings. Frequent MC use was associated with more problems falling asleep and waking up.	There may be a potential tolerance to the sleep-inducing effects of MC with frequent use. Non-randomized study.
8. Linares et al[42]	Crossover double-blind study assessing the effects of a clinically anxiolytic dose of CBD on sleep-wake cycles of healthy subjects (N = 27) receiving 300 mg CBD or placebo.	There was no effect of CBD on sleep architecture noted PSG vs placebo.	Sample size was limited. Further studies are needed in patient populations and with chronic use of different CBD doses.

(continued)

Table 1. (continued)

Study	Design and population	Main results	Conclusions and limitations
9. Devinsky et al[43]	Meta-analysis assessing 4 RCTs of CBD (Epidolex™) with or without clobazam in Lennox-Gastaut and Dravet syndromes.	Epidolex™ was efficacious in reducing seizures with or without clobazam. The incidence of somnolence with Epidolex™ was 32% vs 11% in those on placebo. These effects were dose-related, with a prevalence of 34% in patients who were taking Epidiolex™ at 20 mg/kg/day vs 27% in those on 10 mg/kg/day. Rates of insomnia and poor sleep quality were 5% in patients taking Epidiolex™ at 20 mg/kg/day vs 11% in those on 10 mg/kg/day and 4% in those on placebo.	CBD is associated with somnolence, insomnia, and poor sleep quality. The effects may vary by dose. Sleep was not a primary outcome measure in this study.
10. Nicholson et al[48]	Double-blind, placebo-controlled, 4-way crossover study in N = 8 (4 female, 4 male) healthy subjects 21-34 yo. The 4 conditions were placebo, 15 mg THC, 5 mg THC + 5 mg CBD, 15 mg THC + 15 mg CBD.	15 mg THC appeared to be sedating 15 mg, while CBD appeared to be alerting (increased WASO and counteracted effects of 15 mg THC).	THC products can be sedating. Studies are needed in chronic users of THC and CBD.
11. Arkell et al[50]	Double-blind RCT assessing driving impairment caused by vaporized THC and CBD (each 13.75 mg) in healthy occasional users of cannabis (N = 26).	Measure of lane weaving was significantly higher following vaporized THC-dominant and THC/CBD equivalent cannabis vs placebo at 40-100 min but not 240-300 min after vaporization. These effects were not seen with CBD-dominant cannabis	THC preparations caused significant driving impairment. The CBD-dominant dose tested may not have been reflective of common usage and the effect size reported may not have excluded clinically significant driving impairment.
12. Prasad et al[53]	Proof-of-concept study assessing the effects of increasing doses of dronabinol on AHI in N = 17 subjects with moderate-severe OSA (AHI ≥ 15 events per hour) on PSG performed at baseline, and 7, 14, and 21 days after treatment.	AHI decreased by 14 ± 17.5 ($P = .007$) from baseline to day 21. No changes in sleep architecture or serious adverse events were noted.	The AHI was unchanged or increased in some subjects on dronabinol; therefore, the effects of dronabinol on OSA may be variable.
13. Carley et al[54]	Placebo-controlled, blinded RCT of dronabinol for OSA in N = 73 adults who received placebo, 2.5 mg of dronabinol, or 10 mg of dronabinol for 6 weeks.	AHI at baseline was 25.9 ± 11.3. AHI decreased by 10.7 ± 4.4 ($P = .02$) and 12.9 ± 4.3 ($P = .003$) events/hour at doses of 2.5 and 10 mg/day, respectively. Subjective but not objective measures of sleepiness improved with dronabinol at 10 mg vs placebo.	There was high intra-individual variability in the response to dronabinol and AHI reduction was clinically insufficient.
14. Bonn-Miller et al[59]	Prospective study assessing PTSD symptoms and functioning in a cohort (N = 150, mean age 51 years, 73% male) receiving MC vs controls over 1 year.	MC users reported decrease in PTSD symptoms, including sleep-related symptoms, over the course of 1 year.	Study showed promise with the use of MC in PTSD with improvements in sleep-related and other symptoms.
15. Bonn-Miller at al.[60]	Double-blind crossover RCT assessing the effects of 3 smoked cannabis preparations vs placebo in veterans with PTSD. N = 80 in stage 1 and N = 74 in stage 2 after crossover.	No change in PTSD symptom severity, including that of nightmares, with cannabis preparations vs placebo at the end of stage 1.	There was no effect of CBD on PTSD-related nightmares in this RCT. Further adequately powered RCTs are needed to evaluate the effects of cannabis preparations on PTSD-related sleep symptoms.
16. Chagas et al[61]	Case series (N = 4) describing the effects of CBD on RBD symptoms in patients with PD.	Substantial decrease in frequency of RBD events was noted with CBD without significant side effects.	Small case series showing improvement in RBD frequency with CBD; further large-scale RCTs are required to elucidate the effects of cannabis products in RBD.

(continued)

Table 1. (continued)

Study	Design and population	Main results	Conclusions and limitations
17. de Almeida et al[62]	Phase II/III double-blind, placebo-controlled RCT of CBD (75 or 300 mg) vs placebo in N = 33 patients with RBD and PD followed for up to 14 weeks.	Frequency of nights with RBD, CGI-C, and CGI-S scores did not improve with CBD vs placebo. Sleep satisfaction improved from the fourth to eighth weeks in 300 mg CBD group vs placebo.	This RCT did not show a decrease in RBD frequency with CBD. Further large-scale RCTs are needed to fully elucidate the effects.
18. Megelin and Ghorayeb[63]	Case series of the effects of cannabis in N = 6 patients with RLS.	There was a decrease in RLS symptoms with the use of cannabis.	Small case series suggesting improvement in RLS symptoms with cannabis products. Further large-scale RCTs are required to elucidate the effects.
19. Samaha et al[64]	Single-center survey study of patients (N = 192) with end-stage renal disease, 45% of whom reported RLS symptoms and 67% reported pruritus.	15 patients with RLS reported using cannabis for RLS and/or pruritus symptoms and 9/15 reported improvement.	Some patients reported relief of RLS symptoms with cannabis products. Further large-scale RCTs are needed to fully elucidate the effects.
20. Abrams et al[65]	Crossover RCT assessing the effects of inhaled cannabis vs placebo for pain in patients with SCD over 5 days (N = 23 who completed both arms).	Inhaled cannabis did not decrease pain in patients with SCD vs placebo. There were also no improvements in sleep with cannabis vs placebo.	Further studies are required in patients with a chronic pain manifestation of their RLS to understand effects of cannabis use on symptoms and potential mechanisms underlying these effects. RLS/sleep symptoms were not assessed as a primary outcome in this study with small sample size and brief follow-up duration.

Abbreviations: AHI, apnea-hypopnea index, events per hour; CBD, cannabidiol; CGI-I, Clinical Global Impression-Improvement scale; CGI-S, Clinical Global Impression-Severity scale; MC, medical cannabis; MJ, marijuana; OSA, obstructive sleep apnea; PD, Parkinson's disease; PLM, periodic limb movement; PSG, polysomnogram; PTSD, posttraumatic stress disorder; RBD, rapid eye movement sleep behavior disorder; RCT, randomized controlled trial; REM, rapid eye movement; RLS, restless legs syndrome; SCD, sickle cell disease; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; THC, Δ9-tetrahydrocannabidiol; TST, total sleep time; WASO, wake time after sleep onset.

a decrease in serum concentrations of numerous medications including clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine.[20,21] On the other hand, CBD is a potent competitive inhibitor of CYP2C9, and to a lesser extent, CYP3A4. This may lead a higher International Normalized Ratio (INR) due to an increase in warfarin levels.[22] Clobazem levels can increase by 60% to 500% with concomitant use of CBD but no change has been demonstrated in clonazepam levels.

Effects of Cannabis Use and Withdrawal on Sleep

Cannabinoids and overall effects on sleep. A systematic review and meta-analysis of cannabinoids for medical use showed that nabilone, a cannabinoid that is used as an antiemetic, resulted in improvements in sleep in patients with fibromyalgia.[1] Interestingly, in the medical literature thus far, cannabinoids have been found to improve sleep in studies that were conducted for non-sleep related conditions.[1-4,23-26]

Effects of cannabis on circadian sleep-wake rhythm. Cannabinoids impair normal firing of neurons located in the suprachiasmatic nucleus in mice and may affect the entrainment of the circadian clock to light.[27] Cannabis products may additionally alter the perception of time; this is commonly reported by those who smoke marijuana recreationally.[28] The effects of cannabis products on normal sleep-wake cycles and in those with circadian rhythm sleep-wake phase disorders needs further study.[23,24,29,30]

Effects of cannabis withdrawal on sleep. Sleep disturbances are a hallmark symptom of cannabis withdrawal.[31] Sleep difficulty during attempts to discontinue use of cannabis is reported by 67% to 73% of adults.[5,32,33] Furthermore, sleep difficulty has been consistently rated as one of the most severe symptoms of cannabis withdrawal.[34]

A small case series published in 1975 evaluating the effects of high dose Δ9-THC on sleep patterns found that there was a decrease in SWS on the first night of withdrawal, while REM sleep increased in the 3 days following withdrawal.[35] Another polysomnographic study performed on

days 1, 2, 7, 8, and 13 after abrupt discontinuation of heavy marijuana use showed decreases in TST and REM sleep with increased wake time after sleep onset and periodic limb movements of sleep (PLMs).[36] There was a positive correlation between use of marijuana in terms of number of joints and years of use and the number of PLMs. One study of non-treatment seeking adult cannabis smokers demonstrated that cannabis withdrawal was associated with symptoms that were usually moderate or greater in intensity and often led to alcohol or tobacco use, or relapse to cannabis use.[32]

Effects of Sleep Disturbance on Relapse to Cannabis Use

Sleep difficulty may negatively impact attempts to stop cannabis use as noted in the study by Levin et al[32] described above. In another study, 65% of respondents indicated that sleep difficulty during abstinence contributed to relapse on at least 1 previous quit attempt. In this study, 48% to 77% of subjects reported having resumed cannabis use or used sedative hypnotic drugs, alcohol, or other substances to alleviate their sleep problems.

Effects of Cannabis Products on Sleep Disorders

Effects of cannabis on insomnia. In humans, cannabis can result in an increase in stage 3 non-rapid eye movement or slow wave sleep (SWS), but this has not been shown in all studies as described below, and the effects on rapid eye movement (REM) sleep are variable.[4,5] SWS and REM sleep are considered the deep stages of sleep. Some studies have shown a quicker onset to sleep, subjectively decreased insomnia and nightmares, and increased sleep quality, which appears to decline with chronic use.[5,24,37]

A systematic review was conducted by Gates et al[5] that included a total of 6 studies evaluating the effects of cannabinoid administration on objective sleep measures. This showed that SWS decreased in 3 studies, increased in 1 study, and was unchanged in 1 study. REM sleep was unchanged in 4 studies, increased in 1 and decreased in 1 study. Five of the included studies examined subjective sleep and noted that sleep onset latency decreased with the use of cannabinoids in 3 studies and was unchanged in 1 study. There was no impact on nighttime awakenings. Finally, no dose dependent effects were noted.

Sleep difficulties are commonly cited as a reason that people use medical cannabis. In 1 study, the sales of over the counter (OTC) sleep aids significantly fell once cannabis dispensaries opened in Colorado.[38] However, the evidence supporting its use is weak. There is only 1 randomized controlled trial (RCT) conducted in otherwise healthy patients with insomnia by Cousens and DiMascio,[39] and the remainder are observational studies. In the study by Cousens and DiMascio,[39] THC resulted in a decrease in the sleep onset latency, but it was associated with a "hangover effect" the next morning. In addition, patients experienced temporal disorganization.[39]

A large retrospective case series examining patients at a psychiatric clinic evaluated the impact of CBD on sleep and anxiety. This study showed that anxiety symptoms improved within the first month and remained low for the study duration. At a 1-month follow-up, 66.7% of patients experienced in improvement in sleep and 25% experienced worsening; at 2 months, 56.1% reported improvement and 26.8% reported worsening sleep.[40] Anxiety was measured using the Hamilton- Anxiety (HAM-A) scale and sleep using the Pittsburgh Sleep Quality Index (PSQI). Another crossover study in older adults with chronic pain indicated that sleep maintenance difficulty, but not sleep initiation difficulty or early morning awakenings, improved with the use of medical cannabis after accounting for possible confounders.[41] However, frequent use was associated with more problems with falling asleep and waking at night. Finally, a randomized, double-blinded, placebo-controlled study failed to demonstrate any acute effects of CBD on sleep-wake cycles in healthy subjects.[42]

In controlled studies of patients with Lennox-Gastaut syndrome, the incidence of somnolence and sedation was 32% in Epidiolex™-treated patients, compared with 11% in patients on placebo.[43,44] These effects were noted to be dose-related, with a prevalence of 34% in patients who were taking Epidiolex™ at 20 mg/kg/day, compared with 27% in patients taking it at 10 mg/kg/day. In the same trials, the rates of insomnia and poor sleep quality were 5% in patients taking Epidiolex™ at 20 mg/kg/day, versus 11% in patients taking this at 10 mg/kg/day and 4% in those taking placebo.

In summary, it is challenging to know the effects of cannabis products on insomnia due to significant variations in cannabinoids that are currently available. Research using metabolomic approaches to enhance our understanding of the effects of these products on sleep is increasing to unravel the effects of different strains of cannabis on sleep.

Effects of cannabis on excessive daytime sleepiness. Cannabinoids have been shown to promote wakefulness in a few studies.[45-47] On the other hand, cannabis products are associated with a significant side effect of daytime sedation. One study examined the effects of THC and CBD versus placebo in young adults on subjective measures of nighttime sleep as well as morning sleepiness assessed for 30 min after rising and 9 h after administration of THC and/or CBD.[48] This study showed that 15 mg of THC was sedating, whereas 15 mg of CBD increased wake activity during sleep and counteracted the sedating properties of THC. A meta-analysis showed a significant increased risk (OR 2.10; 95% CI: 1.36-3.31) of fatal motor vehicle collisions with the use of THC.[49] A recent RCT evaluating driving performance in subjects using vaporized Δ9-THC and CBD preparations in on-the-road driving tests showed significantly greater lane departure measures in subjects using THC-containing

preparations 40 to 100 min after vaporization versus those on placebo.[50] The effects of CBD preparations on driving performance were not clear, in part due to the doses used in this study which may not be reflective of commonly used doses. Thus, further investigation is needed to clarify the effects of cannabis products on daytime alertness and if there are predictors of individual variability in the response.

Effects of dronabinol on sleep apnea. Medical marijuana has received approval for the treatment of sleep apnea in some states in the USA. There are some animal studies demonstrating improvement in sleep apnea with cannabis products.[51,52] A proof-of-concept study in humans evaluating the effects of dronabinol at 2.5, 5, and 10 mg showed that the apnea-hypopnea index (AHI), a measure of the severity of sleep apnea, decreased in 5 of 8 subjects and was unchanged or increased in the remainder.[53] In the Pharmacotherapy of Apnea by Cannabimimetic Enhancement (PACE) trial, it is notable that the AHI increased in placebo group; the reduction in AHI in the dronabinol group was slight and would not be considered a clinically significant response.[54] Furthermore, high individual variability to the response to dronabinol was noted in the study.

More research is needed on the effects of cannabis products on sleep disordered breathing.[55] Caution is required with its use in patients with sleep apnea, especially given the possible side effects of cannabis of increased appetite which can lead to weight gain and worsening of sleep apnea and reduced daytime alertness which can further heighten the risks of sleep apnea such as motor vehicle accidents. This is particularly important in the case of sleep apnea, as effective alternative treatment options exist for those who are intolerant of positive airway pressure therapy. The constituents of cannabis products that are currently available vary; specifically, the amount of dronabinol in these products is generally not clear. There are no studies on the effects of dronabinol on sleep apnea in children and adolescents. The American Academy of Sleep Medicine issued a statement opposing the use of cannabis for the treatment of sleep apnea due to unreliable delivery methods and insufficient evidence regarding its efficacy, safety, and tolerability.[56]

Effects of cannabis on posttraumatic stress disorder-related nightmares. There is conflicting evidence regarding the potential benefits of cannabis products in the treatment of PTSD.[57,58] While a long-term study showed some promise in the treatment of PTSD with the use of cannabis products, a recent RCT showed no statistical difference in improvement in PTSD symptoms including nightmares between those assigned to the smoked cannabis group containing various THC and CBD concentrations versus those assigned to placebo.[59,60] Further, there were no improvements in insomnia in the THC or CBD groups compared to the placebo group.

Effects of cannabis on rapid eye movement sleep behavior disorder. A case series described improvement in complex dream enactment behaviors in patients with Parkinson's Disease and RBD.[61] Another study of CBD versus placebo in the treatment of 33 subjects with RBD showed no change in the frequency of nights with abnormal dream enactment behavior, but a transient increase in sleep satisfaction was noted with CBD at 300 mg.[62]

Effects of cannabis on restless legs syndrome. There are some case series reporting improvement in RLS symptoms with the use of cannabis products.[63,64] Cannabis products have potential analgesic properties for those with a chronic pain manifestation of their RLS symptoms; additional mechanisms may relate to the anxiolytic and/or sedative hypnotic effects of these products but are generally unknown at this time.[65,66] There is a lack of objective efficacy measures with the use of cannabis for RLS in the literature. Therefore, caution is recommended with use of cannabis products in RLS, given the limited evidence base and potential for abuse and psychoactive effects.

Conclusions

There has been a substantial increase in the availability and marketing of cannabis products to help with sleep in recent years. Small improvements in subjective sleep were reported with the use of cannabis products in some prior reviews of subjects with chronic pain, such as in patients with multiple sclerosis, peripheral neuropathic, or rheumatoid arthritis-related pain.[25,26] However, similar to most previous reviews, our comprehensive review showed that there is little to no convincing evidence to show that cannabis products lead to significant or meaningful improvements in sleep disorders, including insomnia and RLS. Most studies included in this review were observational in nature, although some RCTs were available. Sleep measures were mostly based on self-report. Cannabis products have been demonstrated to be ineffective for RBD. Dronabinol can decrease the AHI slightly in those with sleep apnea, but this effect is not clinically meaningful. On the other hand, withdrawal from the use of cannabis can lead to significant sleep disruption and relapse to cannabis use. Furthermore, cannabis products can result in daytime sleepiness and impair driving capacity. The concerns with the use of OTC CBD products pertain to the overall lack of evidence that these help with sleep, possible drug interactions, and contamination with Δ9-THC with its attendant psychoactive effects as well as the potential for dependence and other side effects. Clinicians should assess the patient's willingness to have a discussion regarding the use of cannabis products and sleep, emphasize the lack of efficacy of these products for sleep, discuss alternative treatments and risks of cannabis products, and consider harm minimization, as appropriate.

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References

1. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313:2456-2473.
2. Spanagel R, Bilbao A. Approved cannabinoids for medical purposes – comparative systematic review and meta-analysis for sleep and appetite. *Neuropharmacology*. 2021;196:108680.
3. Suraev AS, Marshall NS, Vandrey R, et al. Cannabinoid therapies in the management of sleep disorders: a systematic review of preclinical and clinical studies. *Sleep Med Rev*. 2020;53:101339.
4. Babson KA, Sottile J, Morabito D. Cannabis, cannabinoids, and sleep: a review of the literature. *Curr Psychiatry Rep*. 2017;19:23.
5. Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. *Sleep Med Rev*. 2014;18:477-487.
6. Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev*. 2008;12:381-389.
7. Bonaccorso S, Ricciardi A, Zangani C, Chiappini S, Schifano F. Cannabidiol (CBD) use in psychiatric disorders: a systematic review. *Neurotoxicology*. 2019;74:282-298.
8. Angarita GA, Emadi N, Hodges S, Morgan PT. Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review. *Addict Sci Clin Pract*. 2016;11:9.
9. Garcia AN, Salloum IM. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: a focused review. *Am J Addict*. 2015;24:590-598.
10. Edwards D, Filbey FM. Are sweet dreams made of these? Understanding the relationship between sleep and cannabis use. *Cannabis Cannabinoid Res*. 2021;6:462-473.
11. Mejia-Gomez J, Phung N, Philippopoulos E, Murphy KE, Wolfman W. The impact of cannabis use on vasomotor symptoms, mood, insomnia and sexuality in perimenopausal and postmenopausal women: a systematic review. *Climacteric*. 2021;24:572-576.
12. U.S. Food & Drug Administration. Warning letters and test results for cannabidiol-related products. Accessed December 15, 2021. https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products
13. MJBizDaily. Chart: can medical marijuana programs survive in states with recreational markets? Accessed December 15, 2021. https://mjbizdaily.com/chart-can-medical-marijuana-programs-survive-in-states-with-recreational-markets
14. Ramesh D, Schlosburg JE, Wiebelhaus JM, Lichtman AH. Marijuana dependence: not just smoke and mirrors. *ILAR J*. 2011;52:295-308.
15. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370:2219-2227.
16. Rezkalla S, Kloner RA. Cardiovascular effects of marijuana. *Trends Cardiovasc Med*. 2019;29:403-407.
17. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet*. 2009;374:1383-1391.
18. Huang L, Zhang X, Xu A. Marijuana use for women: to prescribe or not to prescribe. *Subst Use Misuse*. 2020;55:2076-2077.
19. Ghasemiesfe M, Barrow B, Leonard S, Keyhani S, Korenstein D. Association between marijuana use and risk of cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2:e1916318.
20. Antoniou T, Bodkin J, Ho JM. Drug interactions with cannabinoids. *CMAJ*. 2020;192:E206.
21. Brown JD, Winterstein AG. Potential adverse drug events and drug-drug interactions with medical and consumer cannabidiol (CBD) use. *J Clin Med*. 2019;8:989.
22. Grayson L, Vines B, Nichol K, Szaflarski JP. An interaction between warfarin and cannabidiol, a case report. *Epilepsy Behav Case Rep*. 2018;9:10-11.
23. Kaul M, Zee PC, Sahni AS. Effects of cannabinoids on sleep and their therapeutic potential for sleep disorders. *Neurotherapeutics*. 2021;18:217-227.
24. 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;27:383-401.
25. Conroy DA, Arnedt JT. Sleep and substance use disorders: an update. *Curr Psychiatry Rep*. 2014;16:487.
26. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers*. 2007;4:1729-1743.
27. Acuna-Goycolea C, Obrietan K, van den Pol AN. Cannabinoids excite circadian clock neurons. *J Neurosci*. 2010;30:10061-10066.
28. Atakan Z, Morrison P, Bossong MG, Martin-Santos R, Crippa JA. The effect of cannabis on perception of time: a critical review. *Curr Pharm Des*. 2012;18:4915-4922.
29. Vaseghi S, Arjmandi-Rad S, Nasehi M, Zarrindast MR. Cannabinoids and sleep-wake cycle: the potential role of serotonin. *Behav Brain Res*. 2021;412:113440.
30. Fernández-Ruiz J, Galve-Roperh I, Sagredo O, Guzmán M. Possible therapeutic applications of cannabis in the neuropsychopharmacology field. *Eur Neuropsychopharmacol*. 2020;36:217-234.
31. Zhand N, Milin R. What do we know about the pharmacotheraputic management of insomnia in cannabis withdrawal: a systematic review. *Am J Addict*. 2018;27:453-464.
32. Levin KH, Copersino ML, Heishman SJ, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug Alcohol Depend*. 2010;111:120-127.

33. Bolla KI, Lesage SR, Gamaldo CE, et al. Sleep disturbance in heavy marijuana users. *Sleep*. 2008;31:901-908.
34. Kesner AJ, Lovinger DM. Cannabinoids, endocannabinoids and sleep. *Front Mol Neurosci*. 2020;13:125.
35. Feinberg I, Jones R, Walker JM, Cavness C March J. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther*. 1975;17:458-466.
36. Bolla KI, Lesage SR, Gamaldo CE, et al. Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. *Sleep Med*. 2010;11:882-889.
37. Bhagavan C, Kung S, Doppen M, et al. Cannabinoids in the treatment of insomnia disorder: a systematic review and meta-analysis. *CNS Drugs*. 2020;34:1217-1228.
38. Doremus JM, Stith SS, Vigil JM. Using recreational cannabis to treat insomnia: evidence from over-the-counter sleep aid sales in Colorado. *Complement Ther Med*. 2019;47: 102207.
39. Cousens K, DiMascio A. (-) Delta 9 THC as an hypnotic: an experimental study of three dose levels. *Psychopharmacologia*. 1973;33:355-364.
40. Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in anxiety and sleep: a large case series. *Perm J*. 2019;23:18-41.
41. Sznitman SR, Vulfsons S, Meiri D, Weinstein G. Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. *BMJ Support Palliat Care*. 2020;10:415-420.
42. Linares IMP, Guimaraes FS, Eckeli A, et al. No acute effects of cannabidiol on the sleep-wake cycle of healthy subjects: a randomized, double-blind, placebo-controlled, crossover study. *Front Pharmacol*. 2018;9:315.
43. Devinsky O, Thiele EA, Wright S, et al. Cannabidiol efficacy independent of clobazam: meta-analysis of four randomized controlled trials. *Acta Neurol Scand*. 2020;142:531-540.
44. Highlights of prescribing information for Epidolex (cannabidiol) oral solution. Accessed December 15, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
45. Murillo-Rodriguez E, Pastrana-Trejo JC, Salas-Crisóstomo M, de-la-Cruz M. The endocannabinoid system modulating levels of consciousness, emotions and likely dream contents. *CNS Neurol Disord Drug Targets*. 2017;16:370-379.
46. Mijangos-Moreno S, Poot-Aké A, Arankowsky-Sandoval G, Murillo-Rodríguez E. Intrahypothalamic injection of cannabidiol increases the extracellular levels of adenosine in nucleus accumbens in rats. *Neurosci Res*. 2014;84:60-63.
47. Murillo-Rodríguez E, Sarro-Ramírez A, Sánchez D, et al. Potential effects of cannabidiol as a wake-promoting agent. *Curr Neuropharmacol*. 2014;12:269-272.
48. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol*. 2004;24:305-313.
49. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ*. 2012;344:e536.
50. Arkell TR, Vinckenbosch F, Kevin RC, Theunissen EL, McGregor IS, Ramaekers JG. Effect of cannabidiol and δ9-tetrahydrocannabinol on driving performance: a randomized clinical trial. *Jama*. 2020;324:2177-2186.
51. 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:e111412.
52. Calik MW, Carley DW. Effects of cannabinoid agonists and antagonists on sleep and breathing in Sprague-Dawley rats. *Sleep*. 2017;40:zsx112.
53. Prasad B, Radulovacki MG, Carley DW. Proof of concept trial of dronabinol in obstructive sleep apnea. *Front Psychiatry*. 2013;4:1.
54. Carley DW, Prasad B, Reid KJ, et al. Pharmacotherapy of apnea by cannabimimetic enhancement, the pace clinical trial: effects of dronabinol in obstructive sleep apnea. *Sleep*. 2018;4:zsx184.
55. Kolla BP, Mansukhani MP, Olson EJ, St Louis EK, Silber MH, Morgenthaler TI. Medical cannabis for obstructive sleep apnea: premature and potentially harmful. *Mayo Clin Proc*. 2018;93:689-692.
56. Ramar K, Rosen IM, Kirsch DB, et al. Medical cannabis and the treatment of obstructive sleep apnea: an american academy of sleep medicine position statement. *J Clin Sleep Med*. 2018;14:679-681.
57. Steenkamp MM, Blessing EM, Galatzer-Levy IR, Hollahan LC, Anderson WT. Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: a literature review. *Depress Anxiety*. 2017;34:207-216.
58. Orsolini L, Chiappini S, Volpe U, et al. Use of medicinal cannabis and synthetic cannabinoids in post-traumatic stress disorder (PTSD): a systematic review. *Medicina (Kaunas)*. 2019;55:525.
59. Bonn-Miller MO, Brunstetter M, Simonian A, et al. The long-term, prospective, therapeutic impact of cannabis on post-traumatic stress disorder. *Cannabis Cannabinoid Res*. Published online December 9, 2020. doi:10.1089/can.2020.0056
60. Bonn-Miller MO, Sisley S, Riggs P, et al. The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: a randomized cross-over clinical trial. *PLoS One*. 2021;16:e0246990.
61. Chagas MH, Eckeli AL, Zuardi AW, 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 Ther*. 2014;39:564-566.
62. de Almeida CMO, Brito MMC, Bosaipo NB, et al. Cannabidiol for rapid eye movement sleep behavior disorder. *Mov Disord*. 2021;36:1711-1715.
63. Megelin T, Ghorayeb I. Cannabis for restless legs syndrome: a report of six patients. *Sleep Med*. 2017;36:182-183.
64. Samaha D, Kandiah T, Zimmerman D. Cannabis use for restless legs syndrome and uremic pruritus in in patients treated with maintenance dialysis: a survey. *Can J Kidney Health Dis*. 2020;7:2054358120954944.
65. Abrams DI, Couey P, Dixit N, et al. Effect of inhaled cannabis for pain in adults with sickle cell disease: a randomized clinical trial. *JAMA Netw Open*. 2020;3:e2010874.
66. Graczyk M, Łukowicz M, Dzierzanowski T. Prospects for the use of cannabinoids in psychiatric disorders. *Front Psychiatry*. 2021;12:620073.