INVITED REVIEW

Therapeutic Uses of Cannabis on Sleep Disorders and Related Conditions

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Summary: Marijuana generally refers to the dried mixture of leaves and flowers of the cannabis plant, and the term cannabis is a commonly used to refer to products derived from the *Cannabis sativa* L. plant. There has been an increasing interest in the potential medicinal use of cannabis to treat a variety of diseases and conditions. This review will provide the latest evidence regarding the medical risks and potential therapeutic benefits of cannabis in managing patients with sleep disorders or those with other medical conditions who commonly suffer with sleep disturbance as an associated comorbidity. Published data regarding the effects of cannabis compounds on sleep in the general population, as well as in patients with insomnia, chronic pain, posttraumatic stress disorder, and other neurological conditions, will be presented. Current trends for marijuana use and its effects on the economy and the implications that those trends and effects have on future research into medical cannabis are also presented.

Key Words: Cannabis, Medical marijuana, Insomnia, Sleep apnea, Sativex, Dronabinol, THC.

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ABC'S OF CANNABIS: COMMON TERMS AND FORMULATIONS

The *Cannabis sativa* L. plant contains approximately 113 chemical compounds known as cannabinoids. The two cannabinoid components of greatest interest include cannabidiol (CBD) and tetetrahydrocannabinol (THC). CBD is a major cannabinoid that comprises 40% of the plant without any known psychoactive effects, whereas THC, the other primary cannabinoid, does have psychoactive properties. Other cannabinoids in the *C. sativa* L. plant include β-caryophyllene, cannabigerol, cannabinol, and other endocannabinoids. In addition, cannabinoids have been synthetically manufactured. Two major synthetic cannabinoid substances are dronabinol (synthetic THC) and Sativex (synthetic THC and CBD) (Fig. 1).

There are numerous formulations and methods of consumption for cannabis-based products. The most commonly used formulation is herbal cannabis, for which a user smokes the dried plant via a hand pipe, water pipe, rolling paper, hookah, or vaporizer. Hashish is another formulation drawn from Kief, the resin taken from the glands covering the cannabis flower. Hashish can be eaten, smoked or vaped. Before cannabis prohibition, consuming tinctures was the primary mode of consumption for medical uses. It is liquid dissolved in a solvent such as alcohol, vinegar, or glycerol and has the advantage of fast administration and low irritation to body. Hash oil is a tar-like substance similar to oil, eaten directly or put into capsules. A user can infuse or mix cannabis products with other foods. Cannabis extract can also be formulated as lotion and applied topically.

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CENTRAL NERVOUS SYSTEM AND CANNABIS: NEUROBIOLOGY AND MECHANISMS OF ACTION

Cannabis affects the brain by acting upon areas with high to moderate levels of cannabinoid receptors (Fig. 2). Cannabinoid receptors type 1 are expressed at high to moderate levels throughout the brain. Central nervous system regions with high density of cannabinoid receptors type 1 include the cerebral cortex, prefrontal cortex, basal ganglia, cerebellum, and hippocampus. Many of these same regions also play active roles in sleep–wake regulation and other high-order executive functions that include cognition, memory, and posture (Fig. 2). The different cannabinoids have different mechanisms of action. The psychoactive effects of THC are mediated by alterations in the release of central nervous system neurotransmitters such as L-glutamate, gamma-aminobutyric acid, noradrenaline, dopamine, 5-hydroxytryptamine receptors, and acetylcholine. Cannabinol has similar but less potent psychoactive effects than THC. CBD, β-caryophyllene and cannabigerol are nonpsychoactive substances. β-Caryophyllene has potential antiinflammatory properties, whereas cannabigerol has been identified as a possible treatment option for glaucoma (Fig. 2).

CANNABIS AND SLEEP ARCHITECTURE: IMPACT AND INTERACTION

Human adult sleep consists of two phases, non–rapid eye movement sleep and rapid eye movement (REM) sleep that the individual alternately cycles through during the night. Most adults spend 20% to 25% of their total sleep time in REM sleep. During non-REM, there are three stages that reflect successive stages of sleep depth with the majority spent in stage 2 (N2) sleep followed by stage 3 (N3). Both REM sleep and stages N2 and N3 have been associated with both medical and mental restorative properties. Thus, any disruption in the proportion or cycling of sleep through these important sleep stages has been associated

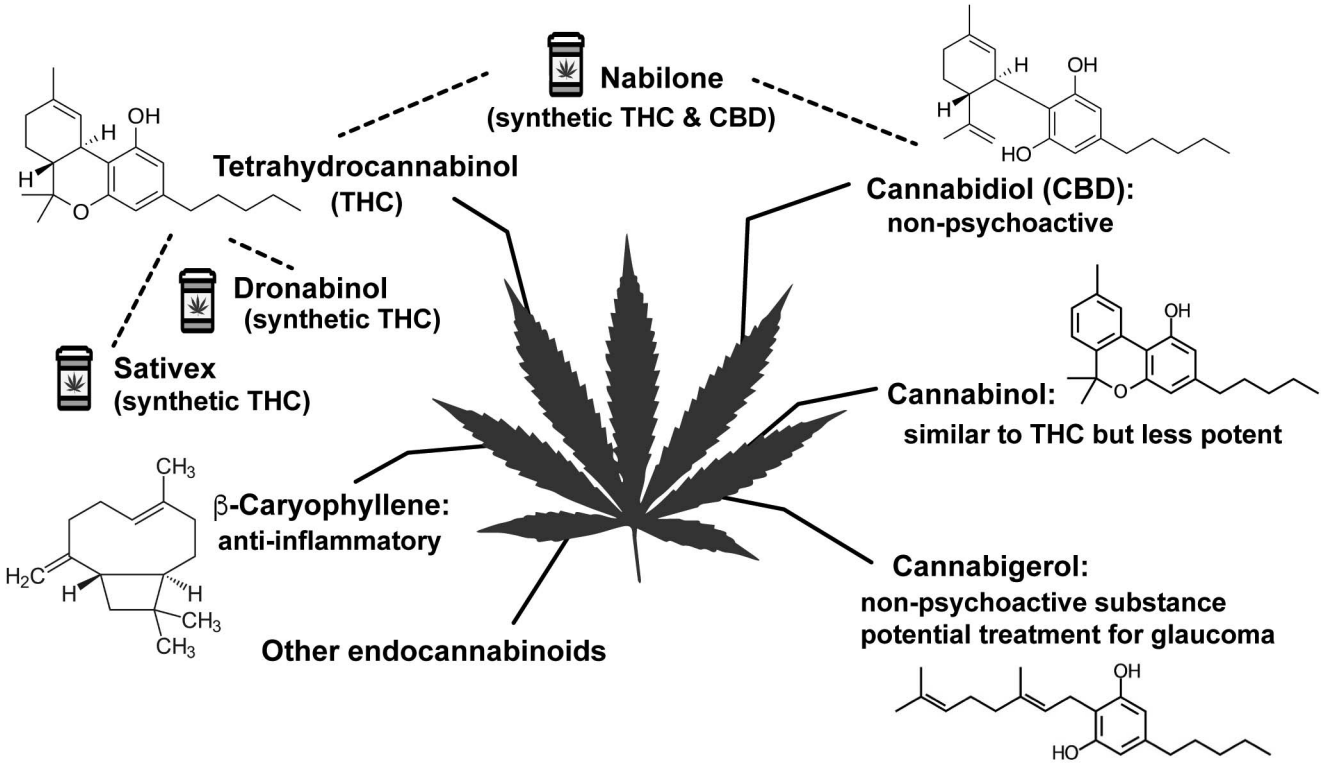

FIG. 1. The main components of the cannabis plant.

with poor sleep quality along with both short-term impact on daytime function and long-term impact on morbidity and mortality. There have been studies suggesting both beneficial and harmful effects of cannabis and cannabis-related products on sleep. These studies have investigated various types of (synthetic and nonsynthetic) cannabis compounds and routes of administration. However, because of the variability in sample size and methodology (variability in the forms of cannabis and routes of administration), firm conclusions on the directionality of this potentially therapeutic relationship remain unclear.

EFFECTS OF CANNABIS ON SLEEP IN GENERAL POPULATION

The impact of THC on sleep quality and architecture in the general population has delivered mixed results (Table 1). One study noted that there is no difference in latency, quality, and nocturnal awakenings compared with placebo group.[1] However, a more recent, double-blind, placebo-controlled study reported that subjects receiving 15 mg of THC and 15 mg of CBD had decreased stage 3 (N3) sleep and increased awake time. In addition, the next day, these same subjects reported increased sleepiness with fatigue and changes in mood. However, the same study found that administering 15-mg THC alone had no impact on sleep.[2] A third study showed that in one subject, THC increased REM sleep at 300 μg/kg, but in two other subjects, it decreased their REM sleep[3] yet increased their percentage of time spent in slow wave sleep (N3).

The potential impact of CBD on sleep architecture has also been reported in the rodent model. In one study, researchers first conducted experiments on rats divided into three groups (control, single dose of 20 mg/kg of CBD, and single dose of 40 mg/kg of CBD). Both the 20 and 40 mg/kg concentrations demonstrated significantly decreased slow wave sleep (N3) latency. In addition, the 40 mg/kg group demonstrated decreased wakefulness and increased time in N3. However, neither REM latency nor the number of REM periods was significantly different between the groups. In a follow-up study, the researchers conducted a second set of experiments where they administered 40 mg/kg CBD to rats daily for 15 days, and compared that with a control group, and found that the chronic administration of CBD had no effect on any of the measures of sleep.[4]

Other studies conducted in animal models showed the opposite directionality in sleep architecture after the administration of CBD. For example, Murillo-Rodriguez et al.[5] also found that microinjection of CBD in wake-inducing areas of the rat brain enhances wakefulness and reduces slow wave sleep (N3) and REM sleep. Similar results were observed in another double-blind, placebo-controlled, human study with a four-way crossover design, which showed that CBD consumption (combined with THC) increases wake time.[2] These mixed and contradictory results may be due the fact that many of these studies are observational or single blind with limited sample sizes. Therefore, more studies on the effects of both short-term

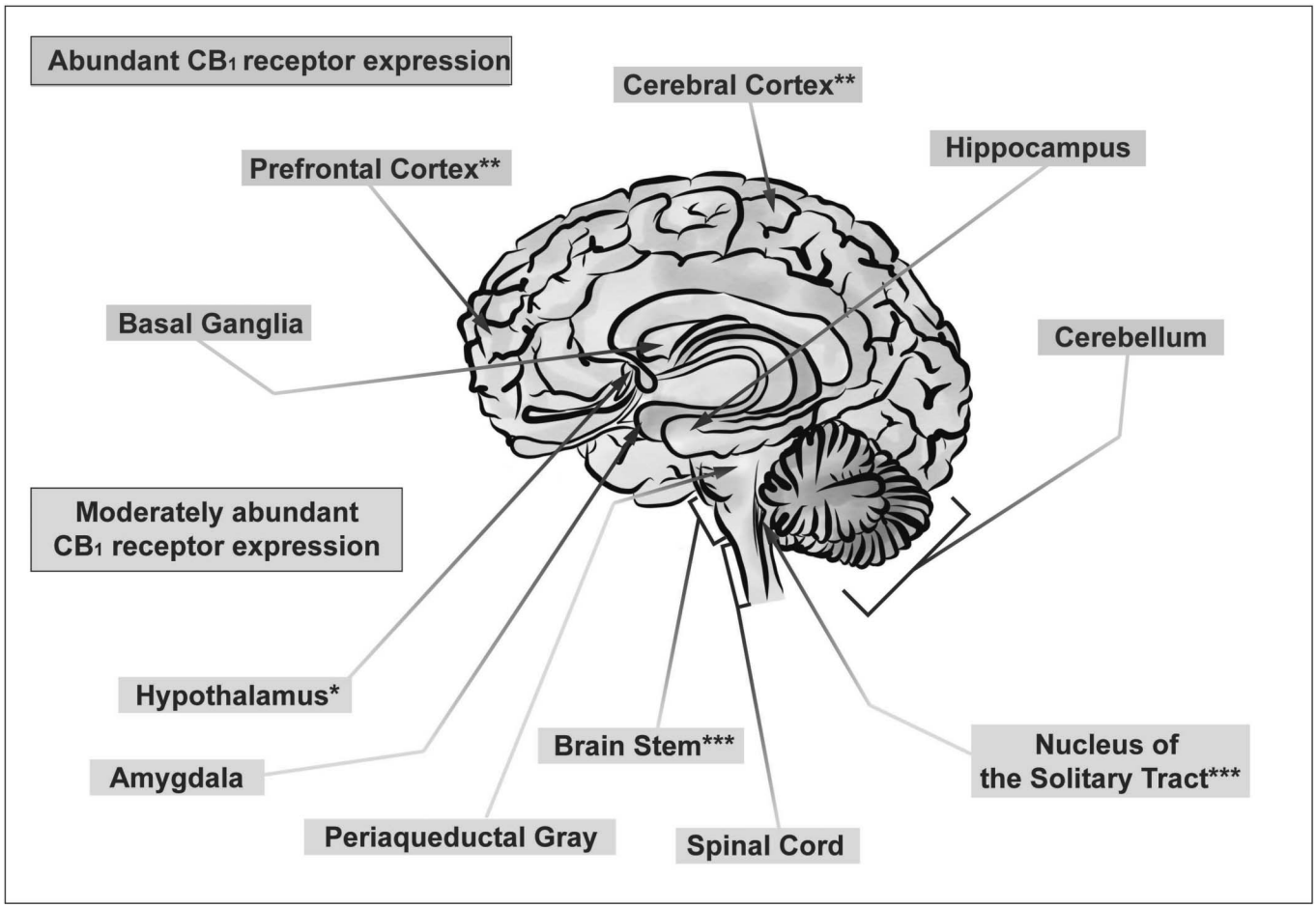

FIG. 2. Locations of CB_1 cannabinoid receptors in the brain.

and long-term cannabis consumption on sleep in the general population are needed. Nonetheless, despite the question of directionality regarding the influence of cannabis compounds on sleep, these studies do suggest that cannabis consumption can impact the sleep–wake cycle and architecture.

THERAPEUTIC USES OF CANNABIS

The use of medicinal cannabis to treat various ailments, including constipation, pain, malaria, epilepsy, and tuberculosis, to name a few dates back to ancient China (Fig. 3) and India. In fact, in the case of ancient India, cannabis appears to have been used as a sleep aid. In the early 1900s, cannabis extracts were first introduced as sedative and hypnotic drugs for the treatment of psychiatric disorders. By the late 1900s, there was a decline in medicinal cannabis use in the Western hemisphere, primarily because of a combination of factors. For one, it was difficult to obtain reproducible effects because the plant was prepared differently in different places around the world mainly because of the unidentified chemically (and medicinally) active components of the plant during that time. Second, new laws and policies, such as the Harrison Act and the Marijuana Tax Act in the United States, resulted in the categorization of Cannabis as a Schedule I illegal substance. The U.S. government had also restricted further research into cannabis that has only relaxed to some degree in the recent years. The characterization of cannabinoid-specific receptors in the nervous system and discovery of endogenous ligands for these receptors have renewed interest in the therapeutic aspects of medical cannabis.

TABLE 1. Effects of Cannabis on Sleep in General Population

Reference Paper	Form of Marijuana	Study Design	Treatments Effect on Sleep
Positive effects			
Karacan et al.[6]	Smoked cannabis	Observational study (no administered THC). A cohort of 32 long-term chronic male marijuana users aged 20–48 years were compared with matched male control subjects, with respect to age (within 5 years), education level, marital status, occupation, frequency and duration of smoking tobacco, and use of alcohol	Marijuana users had greater REM period length but also increased sleep latency, compared with matched control subjects
Monti[4]	CBD	Two sets of experiments: (1) acute experiments in which single doses of 20 and 40 mg/kg of CBD were given; (2) chronic experiments in which once daily injections of 40 mg/kg of CBD were given for a period of 15 days	(1) Decreased SWS latency at 20-mg CBD per kg and decreased SWS latency, increased duration of SWS and decreased wakefulness at 40-mg CBD per kg. No effect on REM sleep was seen with either concentration (2) No effect on sleep overall
Mixed effects			
Hosko et al.[3]	THC	Single-blind placebo. Seven healthy young adult males aged 24–28 years	In one subject, THC increased REM sleep at 300 μg/kg and for two other subjects, increased th percent of time spend in deep sleep (stages 3–4). However, it also showed that for those two last subjects, it also decreased their REM sleep
Barratt et al.[7]	THC	12 males, marijuana smokers, aged 21–26 years	Slow wave sleep increased during first 4 days following marijuana smoking but fell below baseline levels by day 8
Neutral effects			
Chait and Zacny[1]	Smoked cannabis and THC	Two successive trials (one testing effects of smoked cannabis and the other testing effects of THC). Subjects were three female and seven male marijuana smokers, aged 18–30 years	No difference compared with placebo for any component of sleep
Beaulieu[8]	Nabilone (THC derivative)	Double-blind, randomized, placebo-controlled, parallel-group trial; 41 patients (mean age, 52 ± 2 years) undergoing gynecologic (46%), orthopedic (44%), or other (10%) surgery were recruited	Subjects were split up into four treatments: 1-mg nabilone, 2-mg nabilone, 50-mg ketoprofen, or placebo. No difference in sleep was observed in any of the groups
Negative effects			
Nicholson et al.[2]	THC and CBD	Double-blind placebo with 4-way crossover design. Eight healthy volunteers: 4 men and 4 women, aged 21–34 years	Subjects receiving 15-mg THC and 15-mg CBD had decreased stage 3 sleep and increased wake time. The next day, subjects receiving that treatment reported increased sleepiness with fatigue and changes in mood. 15-mg THC alone had no impact on sleep
Murillo-Rodriguez[5]	CBD	Study performed in male Wistar rats	Microinjection of CBD into either lateral hypothalamus or dorsal raphe nuclei, both wake-inducing areas, was able to enhance wakefulness and reduce slow wave sleep and REM sleep. Injection concentration was 10 or 20 μg/μL

CBD, cannabidiol; REM, rapid eye movement; SWS, slow-wave sleep; THC, tetetrahydrocannabinol.

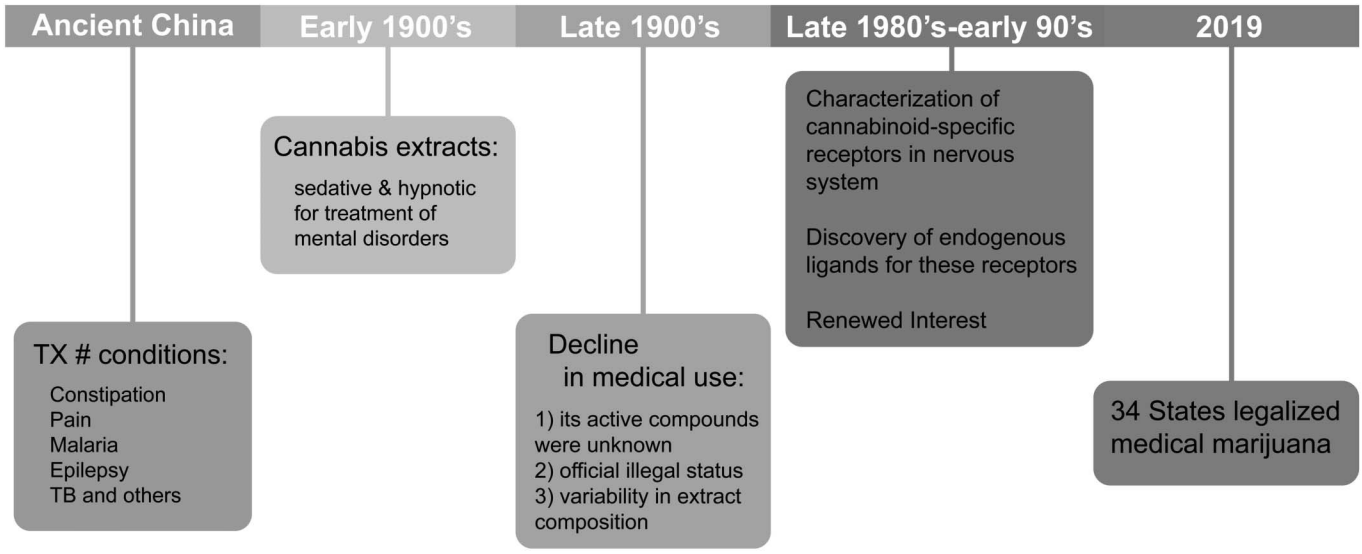

FIG. 3. Timeline of cannabis use in medicine.

The very first Food and Drug Administration (FDA)–approved drug (Epidiolex) that contains any chemical that is naturally found in the cannabis plant (CBD) was approved in mid 2018.[9] Both dronabinol and nabilone, synthetic THC, are also approved by the FDA. Dronabinol is approved for AIDS patients suffering from anorexia, as well as nausea and vomiting associated with cancer chemotherapy in patients who are unresponsive to conventional antiemetic treatments (FDA). Nabilone is FDA approved for the latter.

The literature remains relatively sparse regarding the efficacy of cannabis as a first-, second-, or third-line therapy for sleep disorders in general, and, to-date, the FDA has not approved a cannabis-derived drug that is specifically indicated to treat sleep disorders. More recently, studies have explored the usefulness of cannabis for the treatment of sleep disorders such as insomnia and sleep apnea specifically (Table 2). The main forms of cannabis used in these studies are THC and its derivatives, including delta-9-THC or synthetic compounds such as nabilone and dronabinol. Although the studies remain small in number and sample size (relatively speaking), a fair number have reported improvement in sleep quality metrics for those

TABLE 2. Therapeutic Uses of Cannabis for Treatment of Sleep Disorders

Reference Paper	Form of Marijuana	Treatments Effect on Sleep
Insomnia		
Cousens and DiMascio[10]	Delta 9-THC in liquid form	Decreased sleep latency in healthy insomnia patients
Shannon and Opila-Lehman[11]	CBD oil	Study done on single patient suffering from insomnia because of PTSD. CBD oil reduced insomnia and sleep disturbances in the patient
Tringale and Jensen[12]	Variety of forms	Significant decrease in sleep onset latency in retrospective study of patients suffering from insomnia
Ware et al.[13],†	Nabilone capsule	Study done on fibromyalgia patients suffering from chronic insomnia: Decreased insomnia severity; improved subjective restfulness. No effect on sleep latency and number of awakenings (dose effect was unclear)
Sleep apnea		
Calik et al.[14]	Dronabinol	Intradose ganglion injections of dronabinol alleviate effects of serotonin-induced apnea in Sprague-Dawley rat
Jumpertz et al.[15]	OEA, AEA, and 2-AG—all endocannaboids	Three times higher concentrations of OEA in sleep apnea group suggesting a role of OEA in regulating wakefulness associated with respiratory distress. Serum concentrations of AEA and 2-AG were not significantly different for sleep apnea patients versus control subjects
Prasad et al.[16]	Dronabinol	Reduction in apnea–hypopnea index from baseline
Farabi et al.[17]	Dronabinol	Shift in EEG power toward delta and theta frequencies and strengthening of ultradian rhythms associated with increasing doses of dronabinol

*Not a direct study on insomnia patients, but implications of study point to efficacy regarding treatment of insomnia.
†Also has been shown to treat sleep disturbances because of fibromyalgia.
AEA, anandamide; AG, arachidonyl-glycerol; CBD, cannabidiol; OEA, oleoylethanolamide; PTSD, posttraumatic stress disorder; THC, tetetrahydrocannabinol.

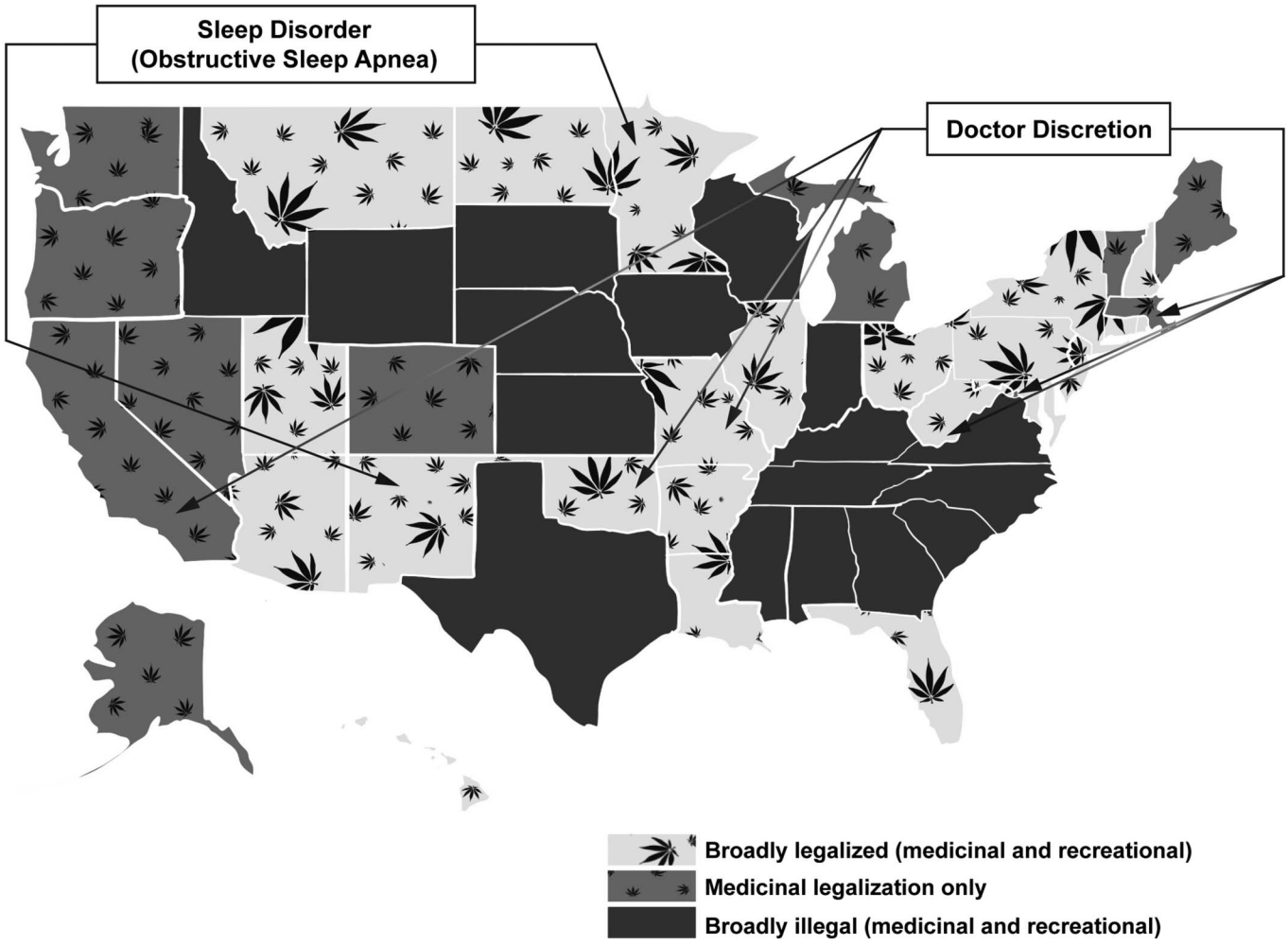

FIG. 4. Cannabis legalization policies for each individual state[18–46] */***Policy information for each state obtained from government agency Web sites of the respective state governments. **Note that these conditions serve as a general list that may vary somewhat state by state and are subject to change. Therefore, please refer directly to the state agency for the most current listing.

individuals suffering with insomnia and sleep apnea. Dronabinol shows promise as a second-line treatment for sleep apnea. One study showed that dronabinol significantly reduces apnea–hypoapnea index compared with placebo, although not to the extent of the positive airway pressure (PAP) devices. Dronabinol was shown to be comparable to PAP devices in the lowering of the Epworth Sleepiness Scale.[45] Because of the limited evidence of efficacy of cannabis-derived therapy for sleep apnea, authors defer to the current published guidelines for treating sleep apnea to the established guidelines of the American Academy of Sleep Medicine.[47] These guidelines do not currently include cannabis-derived therapeutics as a treatment option. Currently, the first-line treatment for sleep apnea is PAP devices, which have been shown to improve the overall quality of life of patients by reducing daytime sleepiness and lowering blood pressure. However, these devices are cumbersome and with outcomes frequently challenged by reduced long-term patient adherence. Thus, identification of PAP alternative options for the treatment of sleep apnea remains an area of interest. One study shows that dronabinol significantly reduces apnea–hypoapnea index. As a result, these reports served as the basis for certain states to include sleep disorders as an approved condition eligible for medicinal cannabis treatment (Fig. 4).

There have been multiple studies that focus on cannabis as a first-, second-, or third-line therapy in treatment of chronic neuropathic pain, a common comorbidity of sleep disorders. Cannabis has gained greater attention in recent years as a possible opiate treatment alternative in the face of the U.S. opiate crisis. Cannabis is not currently recommended as a first- or second-line treatment for chronic neuropathic pain,[48] but one study suggests that cannabis may be used as an adjunctive treatment if first- or second-line treatments have failed.[49] Moreover, opiates are also known to exacerbate sleep problems, particularly sleep apnea. Therefore, further studies are warranted to investigate the potential dual benefit cannabis may play as an opiate-sparing therapeutic to treat

TABLE 3. Therapeutic Uses of Cannabis for Sleep Disturbances Caused by Other Medical Conditions

Reference Paper	Form of Marijuana	Treatments Effect on Sleep
Chronic pain		
Toth et al.[50]	Nabilone	Flexible-dose nabilone 1–4 mg/d improved overall quality of sleep as defined by an 11-point NRS, for patients with diabetic peripheral neuropathic pain
Narang et al.[51]	Dronabinol	Two phase study on patients suffering from chronic noncancer-related pain. Patients receiving dronabinol reported less sleep-interfering pain, as measured by the Brief Pain Inventory
Blake et al.[52]	Sativex	Increased sleep quality (dose effect was unclear) in patients suffering from pain caused by rheumatoid arthritis
Portenoy et al.[53]	Sativex	Decreased sleep disruption on low dose (1–4 sprays per day) and medium dose (6–10 sprays per day). No effect seen with high dose (11–16 sprays per day). Patients had cancer and were on opioid treatment and suffered from chronic pain
Notcutt et al.[54]	Oral spray dose of THC or CBD alone, or THC combined with CBD	Percentage of "good" nights favored THC with CBD (55.4%), over THC (42.9%), CBD (36.9%), and placebo (17%). THC:CBD, THC, and CBD were all significantly more than placebo
Ware et al.[13]	THC joints	Improved subjective sleep latency and sleep restoration on high-dose (9.4%) THC joints only; no effect on number of night time awakenings and sleep quality. Patients were suffering from chronic neuropathic pain
PTSD		
Fraser et al.[55]	Nabilone	Reduction or cessation in nightmares in the nabilone condition for majority (72%) of patients. Some patients reported subjective improvement in sleep duration and quality of sleep and reduction of daytime flashbacks and night sweats
Roitman et al.[56]	Orally absorbable THC (dissolved in olive oil), as an add-on treatment for patients already on other medication	Reduction in nightmares and improvement in sleep quality after THC treatment
MS		
Collin et al.[57]	Sativex	Study conducted on patients suffering from spasticity because of MS. 61% of patients who reported a greater than or equal to 30% improvement in spasticity also reported a greater than or equal to 30% improvement in sleep. Improvement characterized by 0–10 NRS score
Novotna et al.[58]	Sativex, as an add-on therapy	Increased sleep quality (dose effect was unclear), for patients with refractory spasticity caused by MS
HIV		
Bedi et al.[59]	Dronabinol	Sleep efficiency increased in first 8 days of dosing. Study noted that HIV-positive marijuana smokers may require higher doses of dronabinol than approved by FDA because they develop tolerance to it over time
Parkinson disease		
Chagas et al.[60]	CBD	RBD events decreased with use and without significant side effects
Mental disorders		
Cameron et al.[61]	Nabilone	Sleep quality reportedly improved
Primary anorexia		
Gross et al.[62]	Graduating doses of THC capsules	Increased sleep disturbance on THC compared with placebo (dose effect was unclear)

CBD, cannabidiol; MS, multiple sclerosis; NRS, numerical rating scale; PTSD, posttraumatic stress disorder; RBD, REM sleep behavior disorder; REM, rapid eye movement; THC, tetetrahydrocannabinol; FDA, Food and Drug Administration.

TABLE 4. Summary of Potential Therapeutic Benefits for Various Sleep Disturbances

Condition	Potential Therapeutic Benefit
Insomnia	Improved sleep latency and sleep continuity
Sleep apnea	Treatment alternative in those unable or unwilling to adhere to standards of care (e.g., CPAP therapy)
Sleep disturbances secondary to chronic pain	Pain reduction and improved subjective sleep quality
Sleep disturbances secondary to MS-related symptoms	Reduced sleep disruptive spasticity.
Sleep disturbances secondary to HIV-related symptoms	Improved sleep efficiency
Sleep disturbances secondary to Parkinson disease	Reduced sleep disruptive dream enactments because of RBD
Sleep disturbances secondary to PTSD	Reduced nightmare/flashback frequency
Sleep disturbances secondary to affective disorders	Improved sleep quality
Sleep disturbances secondary primary anorexia	Improved sleep quality

CPAP, continuous positive airway pressure; PTSD, posttraumatic stress disorder; RBD, REM sleep behavior disorder; REM, rapid eye movement.

both pain and sleep abnormalities. Similar to chronic pain, cannabis has also been considered for its potential dual benefit in treating the primary symptoms associated with conditions such as such as posttraumatic stress disorder, multiple sclerosis (MS), HIV, Parkinson disease, mental disorders, and the secondary sleep complaints that often accompany them (Table 3). Nabilone and THC showed promising results in treating the recurrent nightmares that are often debilitating for those individuals suffering with posttraumatic stress disorder.[55,56] Two studies suggested that cannabis has beneficial effects on sleep associated with multiple sclerosis.[57,58] Improved sleep was shown among HIV-positive cannabis smokers.[59] In another study, CBD was shown to improve symptoms related to REM sleep behavior disorder in a Parkinson disease cohort.[60]

The studies reporting potential therapeutic benefit of a cannabis-derived treatment (dronabinol) for those suffering with sleep apnea used a capsule delivery formulation. The study reporting the potential benefit of a cannabis-derived therapeutic (specifically Sativex) for the treatment of chronic pain and multiple sclerosis used a nasal spray formulation. For all other conditions, there is no definitive route of delivery that has been reported in the literature to show efficacy in treating sleep or sleep-related disorders. Table 4 summarizes the potential therapeutic role of cannabis in a variety of primary sleep disorders and in medical conditions for which sleep disturbances are a significant comorbidity.

INFLUENCE OF CANNABIS ADDICTION AND WITHDRAWAL ON SLEEP

Cannabis is the most commonly used illicit drug in the United States. More than 20 million people consume cannabis monthly alone (excluding other forms of cannabis) based on a 2015 report by the National Institute of Health.[63] As a result, a sleep provider must be aware of the potential impact that cannabis use and withdrawal can have on their patients' sleep. Cannabis withdrawal has been associated with sleep disruption and insomnia symptoms (Table 5) particularly in studies monitoring heavy cannabis smokers during the acute withdrawal period. Studies have also noted that the symptoms of sleep disruption and rebound insomnia do improve over time, including a study that evaluated a cohort of adolescent users. This finding was independent of affective complaints, drug cravings, or withdrawal symptoms. A study by Gorelick et al.[64] also noted reduced total sleep time in a cohort of daily cannabis users. Interestingly, a 2010 follow-up study by Bolla et al.[65] specifically evaluated heavy marijuana users who reported sleep disruption when previously attempting to abstain from cannabis. The polysomnography recordings in these individuals during an abrupt withdrawal period demonstrated a negative impact on sleep efficiency, total sleep time, wake after sleep onset, REM sleep time, and leg movement activity. It has been noted that heavy marijuana users will often cite poor sleep as the reason for relapse in the setting of abstinence, and thus treating underlying sleep complaints may serve as an effective strategy for cannabis abuse treatment.[65]

CANNABIS AND SLEEP: CLOSING THOUGHTS AND FINAL CONSIDERATIONS

Underlying mechanisms and impact of cannabis on sleep remains somewhat elusive because of the limited number of studies and variability in the design and methods in those reported. As such, well-designed and controlled studies are critical particularly as public policy, federal laws, and medical needs regarding cannabis use and public acceptance views rapidly evolve. Mounting evidence suggests that the use has increased both medically and recreationally over the past 10 years with no signs of reversal. In fact, one study by the Office of National Drug-Control Policy performed drug screens in all male subjects arrested in Atlanta and Chicago in 2013 and found marijuana to be the most common substance to test positive (37% in Atlanta, 58% in Chicago) of all recreational drugs.[66]

Additionally, the increasing use of marijuana could be exacerbated by the sleep deprivation frequently endured among teenagers. One study involving nearly 30,000 teenagers in Fairfax County, VA, found that only 3% of surveyed students

TABLE 5. Influence of Cannabis Use and Withdrawal on Sleep

Reference Paper	Form of Marijuana	Treatments Effect on Sleep
Withdrawal		
Budney et al.[67]	Smoked cannabis	Abrupt discontinuation of treatment effects in heavy marijuana users: self-reports of sleep difficulty (these negative effects are relieved if the subjects resume smoking)
Milin et al.[68]	Unspecified cannabis	Study conducted in adolescents aged 13–19 years. Insomnia symptoms, including sleep difficulties and restlessness, were most pronounced during first two weeks of abstinence, with decreasing severity in weeks 3–4
Levin et al.[69]	Smoked cannabis	Using a retrospective self-report design study, 46.9% of subjects (cannabis users) reported trouble falling asleep during withdrawal during their single most difficult attempt to quit
Wiesbeck et al.[70]	Unspecified	Trouble falling asleep during withdrawal seen in 75.6% of users reporter withdrawal cluster symptoms (multiple symptoms that seem to have a common cause)
Copersino et al.[71]	Smoked cannabis	Retrospective self-report data from adult users who reported at least one serious attempt at quitting; 32% of subjects reported difficulty sleeping during quitting attempt
Gorelick et al.[64]	Marinol (oral THC) capsules	Daily cannabis users provided around the clock THC dosing (in increasing concentration as the study went on) was associated with overall decreased amount of nighttime sleep and increased daytime sleep during 7-day study but also shorter sleep latency
Addiction/long-term smoking		
Bolla et al.[65]	Smoked cannabis	PSG recordings in heavy marijuana users, undergoing acute withdrawal, showed decreases in SE, TST, and REM sleep time and increased amount of PLMs and periods of WASO
Ogeil et al.[72]	Unspecified	Study was done on alcohol and/or cannabis users. Poorer sleep quality was seen in participants deemed to be both heavy (risky) alcohol AND cannabis users compared with nonheavy (nonrisky) users. "Risky" cannabis users were more likely to be poor sleepers per PSQI, use of sleep medications, and report daytime dysfunction

PLM, periodic limb movement; PSG, polysomnography; PSQI, The Pittsburgh Sleep Quality Index; REM, rapid eye movement; SE, sleep efficiency; THC, tetetrahydrocannabinol; TST, total sleep time; WASO, waking after sleep onset.

routinely obtained the recommended 9 to 10 hours of sleep, with most reporting closer to 6.5 hours on average. Moreover, the study also found that for each hour of sleep lost, the likelihood of using marijuana increased by 23%,[73] suggesting a possible association between sleep behaviors and habits and marijuana usage among high school youth.

On the federal level, medicinal cannabis remains under Schedule I classification. Medicinal marijuana is legal in many states, and many states have now also legalized recreational marijuana use (Fig. 4). Doctors cannot "prescribe" marijuana, but instead "recommend" or "refer". The "recommendation/referral" is filled at a regulated medical marijuana legal dispensary in states where medical marijuana is legal. Ongoing consideration must weigh the fact that medical and recreational marijuana has proved be an economic boon for several of the states that have legalized its use which will likely result in other states considering legalization of marijuana for its benefits not only medically but also financially for their state and residents. The economic benefit reported in these states will likely further the discussion regarding the merit both financially and medically to expanding legalization across other states in the United States, warranting greater resources to study the long- and short-term impact of cannabis across various aspects of public and individual health, safety, and economic metrics. As such, there is a strong need to increase the research evaluating the impact of cannabis on the health of the individual, its long-term effects, and how it plays a role in treatments of certain disease in basic, clinical, epidemiology, and public health studies.

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