SLEEP, 2022, 1–14

https://doi.org/10.1093/sleep/zsac218
Advance Access Publication Date: 15 September 2022
Review

REVIEW

Cannabis dosing and administration for sleep: a systematic review

Rob Velzeboer[1,†,*], Adeeb Malas[2,†], Pierre Boerkoel[3], Katie Cullen[3], Michelle Hawkins[3], Jordanna Roesler[4] and Wayne Wei-Ku Lai[5,3]

[1]Clinical Research, Tranq Sleep Care, Kelowna, British Columbia, Canada, [2]Department of Psychiatry, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada, [3]Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada, [4]Department of Dermatology, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada and [5]Medical Director, Tranq Sleep Care, Kelowna, British Columbia, Canada

[†]Contributed equally as first authors.

*Corresponding author. Rob Velzeboer, Clinical Research, Tranq Sleep Care, 215-3030 Pandosy Street, Kelowna, British Columbia, V1Y 1W2, Canada. Email: rob.velzeboer@alumni.lse.ac.uk.

Abstract

Study objectives: As cannabis is increasingly used to treat sleep disorders, we performed a systematic review to examine the effects of cannabis on sleep and to guide cannabis prescribers in their recommendations to patients, specifically focusing on dosing.

Methods: We searched EMBASE, Medline, and Web of Science and identified 4550 studies for screening. Five hundred sixty-eight studies were selected for full-text review and 31 were included for analysis. Study results were considered positive based on improvements in sleep architecture or subjective sleep quality. Bias in randomized controlled trials was assessed using Cochrane Risk of Bias tool 2.0.

Results: Sleep improvements were seen in 7 out of 19 randomized studies and in 7 out of 12 uncontrolled trials. There were no significant differences between the effects of tetrahydrocannabinol and cannabidiol. Cannabis showed most promise at improving sleep in patients with pain-related disorders, as compared to those with neurologic, psychiatric, or sleep disorders, and showed no significant effects on healthy participants' sleep. While subjective improvements in sleep quality were often observed, diagnostic testing showed no improvements in sleep architecture. Adverse events included headaches, sedation, and dizziness, and occurred more frequently at higher doses, though no serious adverse events were observed.

Conclusion: High-quality evidence to support cannabis use for sleep remains limited. Heterogeneity in cannabis types, doses, timing of administration, and sleep outcome measures limit the ability to make specific dosing recommendations.

Statement of Significance

As cannabis is increasingly used to treat sleep disorders, we performed a systematic review of the current evidence to examine the effects of cannabis on sleep and to guide cannabis prescribers in their recommendations to patients, specifically focusing on dosing. We show that cannabis shows most promise at improving sleep for patients suffering from pain-related disorders, and that while patients often subjectively report to feel better about their sleep after using cannabis, diagnostic testing shows that their sleep architecture does not improve in terms of the time it takes to fall asleep, how long they sleep, or the amount of time spent in REM sleep. More high-quality evidence is necessary to make recommendations.

Submitted: 9 May, 2022; **Revised:** 1 September, 2022

Key words: cannabis; cannabidiol; tetrahydracannabinol; CBD; THC; marijuana; sleep; insomnia

Introduction

Cannabis has historically been used for both recreational and medicinal purposes around the world [1]. The origins of cannabis trace back over thousands of years, with evidence of medicinal use dating back to 400 AD [2]. There are many methods of cannabis consumption, including vaporizing, smoking, and oral ingestion of concentrates, oils, and cannabis-containing food products, making cannabis both desirable and convenient [3].

The cannabis plant is incredibly complex; over 400 chemical components, 60 of which are referred to as cannabinoids, have been identified. The main compounds found in cannabis are cannabinol, cannabidiol (CBD), delta-8-tetrahydracannabinol, and delta-9-tetrahydrocannabinol (Δ-9-THC; henceforth THC); its main psychoactive substance [4]. THC and CBD are formed via different enzymatic pathways in the plant and have opposing psychoactive effects [5]. The two main subspecies of the cannabis plant are Cannabis indica and Cannabis sativa. Although in popular literature it is often postulated that Cannabis indicas are higher in CBD than Cannabis sativas and have a more sedating effect, several studies have shown significant hybridization in cannabis cultivation in recent times, leading to more varied concentrations of cannabinoids and no consensus on what differentiates these two species [6–8].

The compounds of cannabis interact with the endocannabinoid system (ECS), which serves important functions including cognitive regulation and physiological processes [9]. The type 1 (CB1) and, less abundant, type 2 cannabinoid (CB2) receptors are G protein-coupled receptors that make up the ECS [2]. Upon ingestion, THC and CBD bind to these receptors [10]. Agonism of the CB1 receptors primarily distributed on presynaptic terminals of neurons impacts multiple neurotransmitter systems including glutamate, acetylcholine, noradrenaline, dopamine, and serotonin [11]. It is postulated that the sedative effect of cannabis stems from the neuromodulation of the partial agonism of THC at the CB1 receptors in the basal ganglia [12, 13]. Although CB2 receptors have also been found in the central nervous system, they are mainly found on immune cells in the spleen, tonsils, thymus, and traveling in the bloodstream [14]. CB2 receptors are activated by endogenous 2-arachidonoylglycerol and are implicated in immunosuppression, inflammation, and pain pathways [15]. Interestingly, CBD is often reported to have a sedative effect although pharmacologically it is an antagonist at both CB1 and CB2 [16, 17].

As a medical treatment, cannabis' first recorded use dates back to ancient China, where it had roles in treating malaria, gout, and epilepsy [18]. Since then, many cultures have recognized the therapeutic potential of cannabis to treat a vast range of ailments. Recently, significant changes in cannabis legalization across North America have resulted in an increasing demand for research on medical cannabis and its health implications [19]. As of October 2018, Canada became the second country in the world to legalize the recreational use of cannabis. Since then, both social acceptability and prevalence of cannabis use have been rising. Near the end of 2020, 20% of individuals aged 15 or older reported cannabis use in the past 3 months. This was significantly higher than the reported use of 14% shortly before legalization in 2018 [20].

Currently, medical cannabis and cannabinoids are used therapeutically across North America for several indications. Approved uses include treating chemotherapy-induced nausea and vomiting, AIDS-related anorexia, and use as an adjunctive treatment for spasticity and neuropathic pain in patients with multiple sclerosis (MS) [21]. While to date neither Health Canada nor the FDA has approved a cannabis-derived drug that is indicated to treat sleep disorders, a benefit often reported by users is subjective improvements in sleep [22]. In fact, in a survey of cannabis users in Canada, 85% reported using medical cannabis therapeutically for sleep [23]. As such, cannabis has been applied to treat a variety of sleep disorders, such as sleep apnea, insomnia, and REM behavior disorder [24–26].

Studies across Europe and North America estimate that approximately 25% of the adult population is dissatisfied with their sleep, with 10%–15% reporting symptoms of insomnia and 6%–10% meeting the criteria for an insomnia disorder [27–30]. Sleep is an important restorative process; physiologically, it is associated with increased rates of protein synthesis and mitotic division [31]. Psychologically, optimal sleep is associated with fewer symptoms of depression and anxiety as well as higher levels of personal growth and purpose in life [32]. More importantly, poor sleep habits have been found to be independently associated with increased all-cause mortality [33]. Symptoms of insomnia, one of the most common sleep disorders, include dissatisfaction with quality or duration of sleep, difficulty falling asleep, daytime fatigue, mood disturbances, and poor cognitive function. At present, short- and long-term therapeutic options for insomnia that are adequately supported by clinical trials include hypnotic drugs and cognitive behavioral therapy [34].

Compared to current pharmaceutical treatments offered for sleep disorders such as benzodiazepines (i.e. lorazepam) or nonbenzodiazepine sedatives (i.e. zolpidem), cannabis offers an advantageous safety profile with minimal toxicity and lethality [35]. However, the use of cannabis is not without risks. Common side effects include dizziness, confusion, and psychomotor impairments, and regular cannabis use can increase the risk of psychosis and addiction, especially for those who initiate use in adolescence [36, 11]. As sleep disturbance is a hallmark symptom of cannabis withdrawal, there can be an increased risk of cannabis dependence for those who use cannabis to manage sleep long-term without proper clinical guidance [37]. In addition, withdrawal can produce irritability, anxiety and depression, headaches, nausea, poor appetite, and insomnia [38, 39]. Despite the widespread use of cannabis as a sleep aid, there is consensus that there currently is insufficient high-quality evidence to support its routine clinical use in treating sleep disorders [35, 40]. However, preliminary findings provide a clear rationale for future research on the safety and efficacy of cannabis for sleep therapy [35].

The lack of specificity of dosing guidelines for cannabis has been highlighted by both researchers and clinicians as an important issue for further investigation [41]. Survey results indicate that most people who use cannabis for medical purposes consume it via oral inhalation or ingestion, and their dosing schedule and timing varies from occasional to daily use [42, 43]. Factors including the concentration of THC and other cannabinoids in cannabis, route of administration, body composition, genetic makeup, and prior food intake all further affect bioavailability, making precise doses difficult to establish [44].