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A new approach to treating sleep disorders? - Medical marijuana review

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Abstract:

Insomnia, defined as difficulty falling or staying asleep, significantly impacts the quality of life and mental health of people worldwide. In recent years, there has been growing interest in using medical marijuana as an alternative treatment method for various conditions, including sleep disorders. The purpose of this review is to examine the available scientific evidence regarding the efficacy and safety of using medical marijuana in the treatment of insomnia. Analyzing data from clinical, observational, and experimental studies, this work aims to present a comprehensive picture of the potential benefits and risks associated with such treatment. This review seeks to provide doctors, patients, and policymakers with up-to-date information that can support the decision-making process regarding the use of medical marijuana as an adjunct therapy in the treatment of insomnia, highlighting both the therapeutic potential and the need for further research in this field.

Keywords: Medical Marijuana; Insomnia; Sleep Disorders

Insomnia- etiology, risk factors, diagnosis, symptoms, treatment and complications

Insomnia, a prevalent sleep disorder, pertains to difficulties initiating or maintaining sleep, or waking up too early without the ability to return to sleep, despite adequate opportunities for sleep. This condition significantly impacts an individual's quality of life, affecting their physical, mental, and emotional health. Epidemiologically, insomnia affects approximately 10-30% of the adult population globally, with variations in prevalence due to demographic factors and diagnostic criteria [1]. It is essential to understand the multifaceted nature of insomnia, including its potential causes, varying manifestations, and its substantial burden on both individual health and public healthcare systems.

The pathophysiology of insomnia is intricate, involving dysregulation within neurobiological systems that manage the sleep-wake cycle. Critical to this process are neurotransmitters like gamma-aminobutyric acid (GABA), which promotes sleep, and

glutamate, associated with wakefulness. Disruptions in their balance can lead to difficulties in initiating and maintaining sleep. Additionally, the circadian rhythm, which regulates the body's internal clock, can become misaligned with external environmental cues, further contributing to insomnia. Stressful life events can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels, which can also disrupt sleep patterns [1,2]. This multifactorial etiology underscores the complexity of insomnia, necessitating a comprehensive understanding for effective management. The main causes of Insomnia are described in Table I.

The reason of Insomnia	Explanation
Neurotransmitter Imbalance	Imbalances in GABA and glutamate affect sleep initiation and maintenance. GABA's reduced activity can lead to difficulty falling asleep, while excess glutamate can prevent staying asleep.
Circadian Rhythm Disruption	Misalignments in the circadian rhythm, influenced by exposure to light, work schedules, and travel across time zones, can lead to significant sleep disturbances, manifesting as insomnia.
Stress and HPA Axis Activation	Chronic stress leads to sustained activation of the HPA axis, elevating cortisol levels, which in turn can disrupt sleep patterns and contribute to the development of insomnia.
Psychological Conditions	Conditions such as anxiety and depression are closely linked with insomnia, often creating a vicious cycle where each exacerbates the other, complicating both treatment and symptomatology.
Environmental Factors	External disruptions like noise, light, and temperature can adversely affect the sleep environment, leading to difficulties in both falling asleep and achieving restful sleep.
Lifestyle Choices	The consumption of stimulants such as caffeine and nicotine, alcohol use, and engaging with electronic devices before bedtime can significantly impair both sleep quality and duration.

Table I. The main causes of Insomnia.

Insomnia symptoms manifest through various sleep disturbances and daytime impairments. Individuals often experience prolonged difficulty in falling asleep despite being tired and frequent awakenings during the night, leading to fragmented sleep. Early morning awakenings are common, with sufferers unable to return to sleep thereafter. This results in a

non-restorative sleep feeling, where one does not feel refreshed upon waking. Daytime consequences include marked fatigue or sleepiness, mood disturbances such as irritability or increased susceptibility to stress, and cognitive impairments, notably in attention, concentration, and memory. These symptoms collectively impair daily functioning, affecting professional, social, and personal aspects of life, leading to a decreased quality of life and heightened risk of accidents or mistakes [1,3].

Complications of insomnia can significantly impact overall health and quality of life. Chronic insomnia may lead to an increased risk of developing mental health disorders, such as depression and anxiety. It can also exacerbate chronic diseases like hypertension and diabetes. Insomnia sufferers often experience impaired cognitive functions, including memory, concentration, and decision-making, affecting their daily productivity and increasing the likelihood of accidents. Furthermore, persistent sleep deprivation is linked to weight gain and a weakened immune system, making individuals more susceptible to infections [4,5].

The diagnosis of insomnia in the ICD-10 is categorized under the section "G47.0 Insomnia". It involves a detailed clinical assessment, including a patient's medical history, sleep patterns, and the impact of sleep difficulties on daily functioning. The criteria focus on difficulties initiating or maintaining sleep, or non-restorative sleep, for at least one month, causing significant distress or impairment in social, occupational, or other important areas of functioning. Additional tests may be conducted to rule out other medical or psychiatric conditions [6]. Diagnostic criteria for insomnia according to ICD-10 are described in Table II.

Diagnostic criteria for insomnia according to ICD-10
-difficulty falling asleep and/or maintaining sleep or sleep that does not bring rest; -symptoms at least 3 times a week and for more than a month; -the symptoms cause significant suffering and/or adversely affect the functioning of everyday life.

Table II. Diagnostic criteria for Insomnia.

For a diagnosis of insomnia to be considered in line with ICD-10 criteria, the sleep disturbances should be present for at least one month. This duration is important to distinguish short-term, situational sleep disturbances from chronic insomnia, which has more significant implications for treatment and management [6].

Treating insomnia involves both pharmacological and non-pharmacological approaches. Behavioral therapies, such as Cognitive Behavioral Therapy for Insomnia (CBT-I), are often the first line of treatment, focusing on changing sleep habits and patterns. Pharmacological treatments may include short-term use of sleeping pills, with options ranging from benzodiazepines to newer sleep aids like zolpidem, eszopiclone, and others. Melatonin receptor agonists and certain antidepressants may also be considered [7]. It's crucial to tailor treatment to the individual's specific needs and underlying causes of insomnia.

Medical Marijuana- basic information, effects on the human body and potential use

Medical marijuana (MM) refers to the use of the Cannabis plant and its chemical constituents, cannabinoids, for therapeutic purposes. The primary chemicals of interest are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), each with distinct structures and pharmacological effects. THC is the main psychoactive component, whereas CBD does not have psychoactive properties and may modulate or counteract the effects of THC. The complex chemistry of cannabis involves over 100 different cannabinoids, contributing to its diverse therapeutic potentials and mechanisms of action in the medical field [8,9].

CBD is a non-psychoactive compound found in the cannabis plant. Unlike THC, CBD does not produce a high or intoxication. It has a variety of potential therapeutic applications, including anti-inflammatory, analgesic, anti-anxiety, and seizure-suppressant properties. CBD is the subject of ongoing research to understand its effectiveness and mechanisms of action in treating various medical conditions [10].

MM has been shown to offer various therapeutic benefits, including pain relief, reduction of inflammation, control of epileptic seizures, and potential anxiety and mood disorder treatments. It may also help with nausea and vomiting in chemotherapy patients and improve appetite in individuals with conditions like HIV/AIDS or cancer. The effectiveness of MM in these areas continues to be the subject of ongoing research and clinical trials [9,11].

Negative effects of MM can include impaired memory and cognition, risk of addiction, potential for increased heart rate, and respiratory issues when smoked. It may also lead to adverse psychiatric effects in vulnerable individuals and interact with other medications. Careful consideration and medical supervision are essential to mitigate these risks [12,13].

MM is used for conditions where it has been found to be effective in relieving symptoms or improving quality of life. Doctors may prescribe it for chronic pain, multiple sclerosis, epilepsy, cancer-related symptoms, and certain mental health conditions like PTSD [14,15]. Its use is dependent on local laws and professional guidelines, with the aim to offer therapeutic benefits where conventional treatments may not have been fully effective.

MM and CBD are increasingly studied for their potential therapeutic effects on psychiatric disorders. Research suggests that CBD, in particular, may have anxiolytic and antidepressant effects, potentially beneficial for conditions such as anxiety and depression [16,17]. However, the relationship between cannabis use and psychiatric disorders is complex, with some studies indicating that excessive or inappropriate use of cannabis may exacerbate symptoms of these conditions or contribute to the onset of disorders in vulnerable individuals [18,19]. Therefore, careful clinical assessment and monitoring are essential when considering cannabis-based treatments for psychiatric disorders.

MM has been explored as a potential treatment for insomnia, with evidence suggesting that its components, particularly CBD, may offer therapeutic benefits by addressing underlying factors such as anxiety and chronic pain that contribute to sleep disturbances [20-26]. While further research is needed to fully understand its efficacy and safety, MM could represent an alternative option for patients seeking relief from insomnia symptoms.

The aim of the review is to gather up-to-date information on the potential use of MM for the treatment of Insomnia.

Materials and Methods

A literature review was conducted following the PRISMA guidelines [27] on January 22, 2024, utilizing the online database PUBMED. The research query was formulated as: "Medical Marijuana AND Insomnia (i) OR Medical Marijuana AND Sleep disorders (ii) OR Medical Cannabis AND Insomnia (iii)". Four hundred sixty (n = 460) results from PUBMED were obtained. After the removal of one hundred forty (n= 140) duplicates, three hundred twenty (n = 320) records were selected for further analysis.

Two independent authors conducted the initial screening of these records. Inclusion criteria were studies published in either Polish or English (a), focusing on the utility of Medical Marijuana as a medical treatment for Insomnia (b). Studies excluded were those

older than 5 years (c), conducted on animal models (d), or in the form of reviews, conference reports, or letters to the editor (e).

Following the selection process, seven ($n = 7$) reports that met these criteria were included for review (Refer to Figure 1).

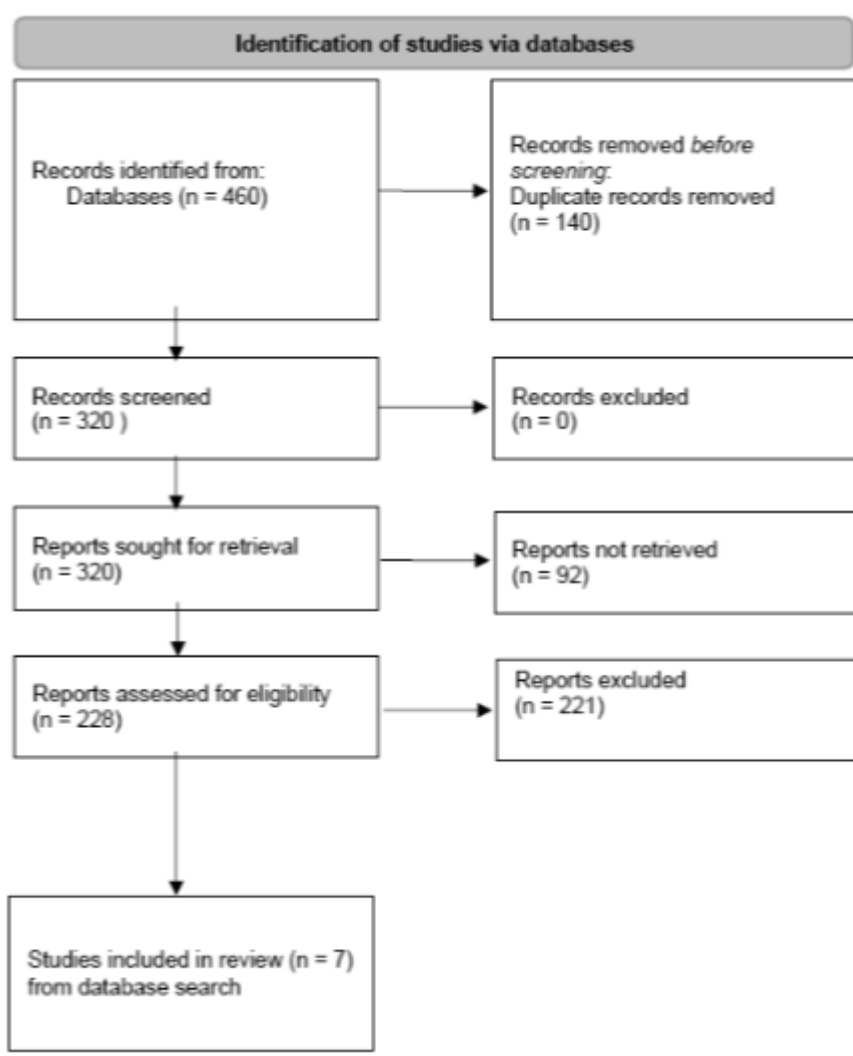


Figure 1. "PRISMA flow-chart"

Results

The results of the review are presented in Table III.

Authors and Year	Sample Size	The research results
Walsh J et al. 2021 [20]	24 patients with chronic insomnia disorder	ZTL-101 notably improved sleep, reducing insomnia severity by 5.07 units and sleep onset by 8.45 minutes, while boosting total sleep by 64.6 minutes, quality by 0.74 units, and morning restfulness by 0.51 units. Night awakenings fell by 10.2 minutes, with sleep duration and efficiency increasing by 33.4 minutes and 2.9%, respectively, as per actigraphy.
Ried K et al. 2023 [21]	29 patients with insomnia	Entoura-10:15 cannabis oil significantly improved sleep quality and duration, with 60% of participants exiting clinical insomnia criteria. Melatonin levels in the active group increased by 30%, in contrast to a 20% decrease in the placebo group. Light sleep duration rose by 21 minutes nightly, and sleep quality improved by up to 80%, enhancing daily functioning. These improvements were more pronounced in the study's second phase.
Vigil J et al. 2018 [22]	406 patients with insomnia	Releaf App™ users reported a symptom severity decrease of 4.5 points on a 0-10 scale, with a significant effect size of 2.10 ($p < 0.001$). Pipes and vaporizers yielded better relief and fewer negative effects than smoking joints. CBD offered greater symptom relief than THC, with CBD levels not affecting side effects significantly. Cannabis sativa flowers had more negative side effects compared to C. indica or hybrids.
Sznitman S et al. 2020 [23]	128 patients with sleep disorders	MC users experienced fewer night awakenings ($p = 0.018$) with no significant variance in other sleep problems. On average, they've used MC for 4 years, consuming 31g monthly, mainly through smoking (68.6%), oil extracts (21.4%), and vaporization (20.0%), with an average of 1.8 strains and THC/CBD levels at 15.6% and 2.84% respectively. Adjusted analyses for demographics and health factors indicated less night awakenings among MC users, without impacting sleep onset or early morning wakefulness. Increased MC use was linked to more sleep disturbances, especially in night awakenings and sleep initiation.
Altman B et al. 2019 [24]	311 patients who reported sleep-related	The study with 309 participants showed significant expectations from cannabis on sleep metrics like falling asleep time, sleep duration, and earlier bedtimes ($p < 0.001$, t-scores 14.12 to 21.75). Significant results had large Cohen's d effects (0.80 to 1.24), suggesting notable benefits like 15 minutes less to fall asleep, 2 more hours of sleep, and going to bed 1.5 hours earlier. Paired t-

	problems	tests confirmed these expectations varied significantly, with the highest for sleep onset time (mean = 1.29) and lowest for wake time (mean = 0.06).
Skobic I et al. 2021 [25]	1639 patients with insomnia	MC usage for sleep was on par with all EBTs at about 5%. Only 0.1% used CBT-I, the top recommended option. Dose changes post-job loss didn't differ significantly between marijuana and EBT users (p = .58). Factors like being male (OR = 0.28) and past substance abuse (OR = 7.68) significantly predicted marijuana use for sleep.
Gilman J et al. 2022 [26]	186 patients with pain or insomnia	In the study, immediate cannabis card access led to more CUD symptoms and reduced insomnia reports but no change in pain, anxiety, or depression symptoms versus delayed access. The immediate access group had a higher CUD rate (17.1% vs 8.6% in the delayed group), particularly in those focusing on anxiety or depression, with a 2.88 adjusted odds ratio for higher CUD incidence.
ZTL-101- is a cannabinoid formulation used in medical research to study its effects on treating insomnia symptoms. THC- tetrahydrocannabinol, CBD- cannabidiol, MC- medical cannabis, CBT-I- cognitive behavioral therapy for insomnia, EBTs- evidence-based psychological treatments, CUD- cannabis use disorder		

Table III. The results of the review.

Discussion

The study conducted at The University of Western Australia's Centre for Sleep Science and sponsored by Zelira Therapeutics Ltd, aimed to evaluate the safety and efficacy of a cannabinoid formulation (ZTL-101) containing THC, CBD, and CBN for treating insomnia symptoms in patients with chronic insomnia disorder. The research design was a double-blind, randomized, placebo-controlled, crossover trial involving 24 participants, predominantly female, with a mean age of 53 years. The study found ZTL-101 to be well-tolerated, significantly improving insomnia symptoms compared to placebo. Key improvements included decreased Insomnia Severity Index scores, reduced sleep onset latency, increased total sleep time, better sleep quality, and enhanced restfulness upon waking. Actigraphy data also showed decreased wake after sleep onset and increased total sleep time and sleep efficiency, highlighting ZTL-101's potential as an effective insomnia treatment. These findings suggest that ZTL-101 could be a promising treatment for chronic insomnia, warranting further investigation in larger studies [20].

In a double-blind, placebo-controlled trial, 29 adults with clinical insomnia evaluated the efficacy and tolerability of Entoura-10:15 medicinal cannabis oil, containing THC and CBD. Over a 2-week treatment phase, with a subsequent 1-week washout before crossover, improvements were noted in sleep quality, melatonin levels, and daily functioning, with 60% of participants exiting clinical insomnia criteria. Saliva tests showed a 30% increase in midnight melatonin levels in the active group, contrasting with a 20% decline in the placebo group. Additionally, light sleep duration increased by 21 minutes per night, and overall sleep quality improved by up to 80%, indicating the oil's potential as an effective insomnia treatment. The trial demonstrated significant enhancements in sleep parameters and was well-received, suggesting medicinal cannabis oil as a promising treatment for insomnia symptoms [21].

In a comprehensive study leveraging a mobile application to monitor real-time effects, 409 individuals with insomnia reported on their cannabis consumption experiences. This investigation uniquely quantified how different characteristics of medical cannabis flower—such as consumption method, cannabinoid content, and plant subtype—affect perceived insomnia severity. Findings indicated a significant reduction in symptom severity, highlighting the nuanced efficacy and side effect profiles of cannabis based on its properties. The study found that using the Releaf App™, participants noted a significant reduction in insomnia severity after consuming medical cannabis. Vaporizers and pipes were preferred over joints for their efficacy and fewer side effects. CBD showed more relief compared to THC, without significant side effect differences. *C. sativa* strains led to more negative effects than *C. indica* or hybrids. These results underscore the importance of specific cannabis characteristics in managing insomnia symptoms effectively. Notably, consumption methods like vaporization and the use of pipes were preferred over joints for their efficacy and fewer adverse effects, underscoring the importance of product selection in managing insomnia symptoms effectively [22].

The other study involved 129 chronic pain patients over 50, comparing medical cannabis users and non-users. Medical cannabis users, younger on average and predominantly male, reported less frequent nighttime awakenings compared to non-users. Both groups showed similar baseline characteristics except for age and gender. Medical cannabis usage patterns varied, with smoking being the most common method. Despite no significant differences in sleep latency and early awakenings, frequent MC use correlated with increased sleep disturbances. The findings suggest MC's potential to improve sleep quality, albeit with

considerations for usage frequency [23].

The research conducted by authors affiliated with the University at Albany, State University of New York, is a cross-sectional study exploring the self-reported effects of cannabis on sleep among 311 individuals. The aim was to understand expectancies regarding cannabis' impact on sleep-related disturbances. The study revealed significant positive expectancies among cannabis users regarding its effects on sleep. Participants anticipated cannabis would help them fall asleep faster, sleep longer, and go to bed earlier. These expectancies were substantiated by large effect sizes, translating into tangible improvements in sleep habits. However, cannabis' influence on morning wake times was not significantly expected. Overall, the findings suggest that individuals perceive cannabis as beneficial for sleep, with varying degrees of expectancy across different sleep-related aspects [24].

Skobic I et al. investigated the prevalence of marijuana use for managing sleep disturbances and relaxation among individuals who recently lost their jobs, comparing it to evidence-based treatments (EBT) like Cognitive Behavioral Therapy for Insomnia (CBT-I), and various sedatives. The study found that marijuana usage was on par with EBTs, with a very low uptake of CBT-I, despite its recommendation as a primary intervention for insomnia [25].

The research utilized data from the ADAPT study, involving 1639 participants, to evaluate the use of marijuana versus evidence-based treatments (EBTs) for sleep/relaxation in individuals facing job loss. Surprisingly, marijuana usage was as prevalent as EBTs, including Cognitive Behavioral Therapy for Insomnia (CBT-I) and certain medications. However, only a minuscule fraction reported using CBT-I, the recommended approach for insomnia. Analysis identified a significant correlation between male gender, substance abuse history, and a higher propensity for marijuana use for sleep issues. The analysis identified male gender and a history of substance abuse as predictors of increased marijuana use. The findings underscore the necessity of expanding access to and awareness of effective sleep health strategies in unemployed groups to mitigate the long-term reliance on marijuana for managing sleep issues [26].

Despite cannabis being legalized for medical use across various regions in the US, the clinical evidence backing its effectiveness for certain conditions is still not comprehensive [27,28]. This study aimed to explore the impact of obtaining a medical marijuana card on clinical outcomes and symptoms of cannabis use disorder in adults with main complaints of chronic pain, insomnia, or anxiety/depression. Conducted in Greater Boston from July 2017

to July 2020, it involved adults randomized into two groups: one receiving immediate access to a medical marijuana card and the other after a delay. The investigation focused on changes in cannabis use disorder symptoms, anxiety, depression, pain severity, and insomnia symptoms [27].

The study's results demonstrated that participants who received a medical marijuana card immediately exhibited increased symptoms of cannabis use disorder (CUD) but experienced significant improvements in self-reported insomnia symptoms, without notable changes in pain, anxiety, or depression levels. Notably, the incidence of CUD was higher in the immediate card acquisition group, particularly among individuals primarily concerned with anxiety or depression. This suggests a complex relationship between access to medical marijuana and its effects on various health outcomes, highlighting the need for further research on its benefits for insomnia and associated risks of CUD. Findings indicated that immediate access led to more cannabis use disorder symptoms but improved insomnia symptoms, with no significant changes in pain, anxiety, or depression. This underscores the need for further research on medical marijuana's benefits for insomnia and its risk of cannabis use disorder, especially in individuals with anxiety or depression [27].

Conclusions

The recent studies on the use of medical marijuana for treating insomnia has yielded promising results, highlighting its potential as a beneficial alternative to traditional sleep aids. Participants in the study experienced improvements in various sleep parameters, including decreased time to fall asleep, increased sleep duration, and fewer instances of waking up during the night. The use of medical marijuana also resulted in a reduction of insomnia symptoms, contributing to enhanced overall sleep quality and better daytime functioning.

While the study supports the efficacy of medical marijuana in improving sleep for individuals with insomnia, it also underscores the need for further research. Additional studies are necessary to fully understand the long-term effects of medical marijuana use for insomnia, its potential tolerance development, and the optimal dosages and methods of consumption for various patient populations [29,30]. Moreover, further research should aim to clarify the mechanisms by which medical marijuana exerts its sleep-promoting effects and to identify any potential risks associated with its use in treating sleep disorders. Overall, while medical marijuana presents a promising treatment option for insomnia, comprehensive and rigorous research is essential to validate these findings and ensure safe and effective use.

Disclosures

Author's contribution:

Conceptualization- Daniel Gondko

Formal analysis- Daniel Gondko, Patrycja Dębiec

Investigation-Patrycja Dębiec, Jakub Roman

Writing-rough preparation-Jakub Roman, Nikodem Pietrzak

Writing-review and editing-Daniel Gondko, Patrycja Dębiec, Nikodem Pietrzak

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