

The Modulating Role of Cannabis in Insomnia: A Review of the Literature

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Abstract

The objective of this study was to carry out a review of the literature covering the topic of the association between sleep, insomnia and the medicinal use of cannabis. The guiding question for carrying out this study was whether the medicinal use of cannabis could have a significant positive impact on reducing insomnia. To this end, a review of the literature on the topic was prepared, both in English and Portuguese, from 2005 to 2023, in the PubMed, Scielo and LILACS databases. To search the databases, the keywords “cannabis”, “cannabidiol”, “tetrahydrocannabinol”, “insomnia” and “endocannabinoid” were used. In total, the initial search resulted in 17 articles. After a more careful analysis, only 6 of these articles met the inclusion criteria established for this study. Thus, it was concluded that, although some studies link the use of medicinal cannabis with an improvement in sleep quality, the current literature still lacks more studies on the topic.

Keywords

Cannabis, Cannabidiol, Tetrahydrocannabinol, Insomnia, Endocannabinoid

1. Introduction

Sleep, which is extremely important for the behavioral and cognitive functioning of human beings, is mainly based on a sleep-wake cycle related to the circadian cycle. The predominant factor in wakefulness is the activity of the tuberomammillary nucleus, dorsal raphe, cerulean locus and posterior hypothalamus. This group is known as the ascending reticular activating system and allows the human being to become awake, this process being promoted by norepinephrine, dopamine, and orexin. Sleep, meanwhile, is an inhibition of the ascending reticular activation system via the ventrolateral preoptic nucleus and the median preoptic nucleus, based

on the release of γ -aminobutyric acid (GABA) and galanin [1]-[3].

However, the sleep-wake cycle doesn't work perfectly in every population, causing insomnia, a hyperarousal disorder manifested as a state of hypervigilance during the day and difficulty in initiating or maintaining sleep at night [4]. Chronic insomnia, according to the DSM-5 and the International Classification of Sleep Disorders (ICSD-3), is the disturbance of sleep onset or continuity, three or more days a week for at least three months that is associated with substantial distress and impairment in daytime functioning [1] [5] [6].

Approximately 10% of the adult population suffers from some kind of chronic insomnia disorder and 20% experience insomnia symptoms occasionally. It is also worth noting that women and the elderly have a higher prevalence of the disease and that other factors such as social issues, personality traits, psychiatric comorbidities and substance use can also be risk factors for acute and chronic insomnia [1] [7].

The prevalence of this disorder is worrying, since the difficulty in falling asleep or staying asleep affects several dimensions of the patient's life, such as physical functioning, the general perception of health, vitality, social functioning, emotional and mental health, which leads to a sudden decrease in the patient's quality of life. In addition, chronic insomnia generates a series of health conditions, such as dysfunction of the hypothalamic-pituitary-adrenal axis, atherosclerosis, and the release of inflammatory mediators. These can culminate in cardiovascular diseases, systemic arterial hypertension, type II diabetes mellitus, gastroesophageal reflux, and asthma [1].

Clinical evaluation for the diagnosis of insomnia and sleep assessment can be carried out using various mechanisms, which can have totally different or similar objectives, contributing to a more accurate diagnosis. Some of the most used mechanisms today are self-reporting using the Insomnia Severity Index (IST), actigraphy, melatonin levels during the night and polysomnography (PSG) [1] [8].

The Insomnia Severity Index (ISI), actigraphy, melatonin levels during the night and polysomnography (PSG) [1] [8] are used to assess various aspects of sleep and contribute to diagnosis. Such as the time between lights out and falling asleep (SOL), the total time spent asleep during the night (TTS), the time spent awake after falling asleep until the final time of getting out of bed (WASO), the proportion of time spent asleep between lights out and getting out of bed (SE), the number of awakenings per hour of sleep, from lights out until getting out of bed (IA), the perceived quality of sleep (sQs).

Given the negative consequences that insomnia can have on a patient's quality of life, there are various forms of therapy and medication that have already been established to treat this disorder and others that are still being experimented with, such as the treatment of insomnia using cannabis. Cannabis was discovered around 12,000 years ago in Central Asia and has since been used in countless ways, with the first records of medicinal use in China [9].

The medicinal use of cannabis is due to the presence of various substances that can be used as herbal medicines for certain pathologies. The plant has more than

100 compounds, but the best known are cannabidiol (CBD) and 49-tetrahydrocannabidiol (THC). Unlike THC, which is mainly used recreationally, CBD can be used in some pathological conditions due to its herbal properties.

CBD has been used as a treatment for insomnia and so far, it is considered a beneficial and safe use, since there have been no reports of overdose with any of the cannabinoids. As for THC, studies covering the treatment of insomnia with cannabis show that the properties of this component reduce sleep onset time and reduce nocturnal awakenings [10].

It is worth noting that the properties of cannabis are not essentially exogenous to the human body, the endocannabinoid system, a neuromodulator network of the central nervous system, regulates various physiological and cognitive processes in the human body. It is made up of endogenous compounds (endocannabinoids), cannabinoid receptors and proteins that transport, synthesize, and degrade these compounds. This allows an endogenous system in the human body to have a direct relationship with various active ingredients in the plant, which is essential for the body to utilize the phytotherapeutic properties of cannabis's active ingredients [11].

It is, therefore, important to understand how cannabis and its compounds can modulate the sleep-wake system, influencing insomnia as an alternative route to drug treatment. The aim of this study is, therefore, to carry out a descriptive literature review to assess the importance of cannabis and cannabidiol in insomnia disorders.

2. Methods

This literature review was conducted by searching databases on the PubMed, Scielo and Lilac platforms. The search was carried out using the following keywords: "cannabis", "cannabidiol".

"THC", "CBD", "insomnia", "sleep disorder". Only original articles in human models were selected, between 2005 and 2023, in English, Portuguese and Spanish. The articles were chosen so that they addressed the respective keywords and aimed to review the effect of the medicinal use of cannabis on insomnia disorder. Clinical trials and randomized clinical trials with these search terms were included in this review article. Studies outside the search period, studies carried out on animal models, review articles or those that did not address the objective of the study were not accepted. In total, 17 articles were found and 12 of them did not proceed, since 6 articles dealing with diseases that did not address sleep (pediatric epilepsy, fibromyalgia, multiple sclerosis and blepharospasm); 4 were excluded because they dealt with cannabis abstinence or continuous use of the substance; 2 dealt with the use of cannabis associated with other non-cannabinoid drugs (nitrazepam, zolpidem); and 1 did not present the experiment in a human model.

3. Results

The selection of studies for this article resulted in four articles that met all the

conditions presented in the methodology. These four articles promote some common concerns, mainly related to health and sleep. In addition, they address the strong link between these sleep disorders and mental health problems, such as depression, anxiety, and other alterations of the psyche. In addition, the articles also address how other factors affect sleep quality, for example, the relationship between sleep and metabolic health. It is also worth noting that they address not only mental problems, but also diseases of the human body and their relationship with sleep. For example, cardiovascular risks combined with sleep deprivation can lead to a propensity to generate heart disease, such as hypertension. Finally, the four articles found an improvement in the quality of sleep, as well as helping to correct sleep disorders, through the use of cannabis.

These were analyzed and will be presented briefly in table form. The following **Table 1** shows the following aspects of the articles: author, extract used, daily dosage of the active compound, duration of the study, and conclusion.

Table 1. Summary of studies on Cannabis and Sleep.

Article	[8]	[12]	[13]	[14]
Extract	Nocturnal sublingual cannabinoid (ZLT-101)	Smoking (medical cannabis cardboard)	Medicinal cannabis oil at night	Smoking
Dosage	0.5-1 mL of ZTL-101	Private choice ^b	0.2 a 1.5 ml/day	Private choice ^b
Period	2 weeks	1 year	6 weeks	4 weeks
Formulation	THC 20 mg/mL, CBN 2 mg/mL, CBD 1 mg/mL	This data was not exposed	10 mg/mL THC, 15 mg/mL CBD, other CBs	This data was not exposed
Participants	23	186	29	56
Test	ISI, actigraphy, PSG and self-report	Self-reported sleep quality	Melatonin, ISI, actigraphy	ISI
Conclusion	Treatment with ZTL-101 ^a over two weeks showed improvement in patients with insomnia and chronic insomnia	The immediate acquisition of a medical cannabis card led to an improvement in self-reported sleep quality	The study with cannabis oil, together with the collection of melanin levels during the night, proved to be effective, contributing to the improvement of patients' quality of sleep	CBT-I (cognitive-behavioral treatment for insomnia) generated an improvement in the reduction of insomnia symptoms, unrelated to cannabis

a. ZLT-101 refers to nocturnal sub-lingual cannabinoid. b. Private choice refers to the way in which the article chose to offer its participants cannabis, *i.e.*, in these articles, the dosage and frequency of cannabis use were chosen by the study participant in question.

A study carried out by Walsh and his collaborators (2021) [8] used a nocturnal

sublingual cannabinoid (ZTL-101) compared to a placebo. 52% of the participants were taking a double dose of ZTL-101 on the 14th night, while 69.9% were taking a double dose of placebo on the 14th night. In the self-report, SOL, TTS, sQs, and resting sensations showed significant improvements in these aspects of sleep. In actigraphy, SOL and IA did not show significant improvements, while TTS, sQs and the feeling of rest, as well as in actigraphy, showed a significant improvement, positively influencing sleep. However, in polysomnography, none of the aspects of sleep mentioned above showed a significant improvement. The article attributes this to the fact that polysomnography, as it is carried out in a hospital environment, is only done once for each participant, and this may influence the results of the study.

Regarding the advantages and disadvantages of Walsh and his collaborators (2021) [8] study, the rigorous methodology used in it allowed for an improvement in the patient's insomnia symptoms, so this methodology ensured that the results were due to the cannabinoids present in ZLT-101. In addition, the study used different forms of sleep assessment and did not present any safety problems with the use of nocturnal sublingual cannabinoids. On the other hand, the sample size was small, and the study was short, limiting the results and not allowing the long-term effects to be assessed. The partial reliance on self-reporting can also be cited as a negative factor.

Regarding the positive and negative points of a study carried out by Gilman and his colleagues (2022) [12], it can be mentioned that the study included a large sample of participants, who were divided into immediate and late card acquisition groups, which made it possible to compare the impact of substance use. The study also presented an improvement in self-reported sleep quality. However, there were also negative points, such as the lack of dosage control (allowing participants to choose the dose they would take), making it difficult to analyze the specific effects of a given cannabinoid. In addition, only self-reported sleep quality was used, and no other forms of sleep assessment were used, which hampered the analysis of the results.

Another study by Ried and his colleagues (2022) [13] used three main evaluators: midnight melatonin level, ISI and actigraphy. Regarding midnight melatonin levels, there was a 30% improvement in the active group, while there was a decrease in the placebo group. Sleep quality, as assessed by the ISI improved significantly in the active group compared to placebo, which was also perceived by an improvement in daily functioning in the active group of up to 80%. Sleep duration measured by actigraphy improved in the active group, with a significant increase in the "light sleep" stage of 21 min/night compared to placebo. It is worth noting that 79% to 89% of the participants had an ISI of moderate to severe clinical insomnia at the start of the study, while at the end of the study, only 35% were patients with clinical insomnia.

Regarding the advantages and disadvantages of this research, the study used the gold standard for clinical trials (randomized, double-blind, and placebo-controlled),

which ensured that the results were reliable and reduced doubts about the study. In addition, the study showed a significant improvement in sleep quality in various tests, such as melatonin level, ISI, and actigraphy. The duration of the treatment (6 weeks, including washout) is also a positive point, making it possible to evaluate the effects in the short and long term. On the other hand, the sample size of the article was small, and there was a heavy reliance on self-reporting, limiting the results and making studies with larger samples necessary to confirm these results. It is also worth pointing out that a one-week washout may not be enough, influencing other results that depend on the washout.

Regarding the positive and negative points of an article by Miller *et al.* (2022) [14], the positive point is that the study focused on a specific population (young people aged 18 to 30), and this allowed for a targeted analysis of the effects of cannabinoid use on insomnia and the effects of cognitive behavioral therapy (CBT-I) for insomnia. On the other hand, the small sample size, the short duration of the study, and the lack of dosage control could lead to uncertainties. In addition, there were contradictory results, and here is the negative point of self-report dependence: while self-reports showed a significant improvement, objective measures of actigraphy did not show the same significance.

4. Discussion

The quality of sleep affects various areas of the physical constitution, such as physical and mental well-being, which results in greater disposition and increased focus on daily activities, both basic and complex. Thus, a good night's sleep is essential for a good quality of life, since sleep deprivation or destabilization has a high negative impact on health [15].

One of the best-known causes of sleep deprivation is insomnia [16]. In this respect, in an effort to improve the quality of sleep in cases of insomnia, tests have been carried out on humans, involving cannabis and the use of some of its active principles [17]. However, even though the discussion involves insomnia and a treatment using cannabis active ingredients, there is still not a large number of articles on the subject. Most clinical trials evaluating the usefulness of cannabinoids in treating sleep disorders, such as insomnia, have a high risk of bias, with small sample sizes and a lack of high-quality, randomized clinical trials involving clinical populations [18].

In this paper, we reviewed 4 articles, which demonstrated important results on the influence of exogenous cannabis on patients diagnosed with insomnia. As shown in the table, three studies found an effect with different routes and doses, but one did not show a result related to cannabis. The work by Gilman [13], despite showing a significant effect, raised an important question about the use of cannabis associated with mood disorders. The patients in this study developed more depression and anxiety symptoms over the course of the experiment. In this sense, its use for insomnia in psychiatric conditions should be evaluated, given that the modulation of receptors and neurotransmitters for sleep and mood occurs

in common areas, through the endocannabinoid system.

As previously mentioned, the endocannabinoid system is directly related to cannabis compounds, since this system is made up of both endogenous compounds (endocannabinoids) and cannabinoid receptors. This system synthesizes and degrades these compounds, which allows the human body to use the herbal properties of cannabis [19]. As shown in **Figure 1**, in addition to regulating sleep, this system plays an important role in appetite, pain reduction, behavior and immunity. In this way, the components of cannabis perform in a similar way by interacting with the same receptors.

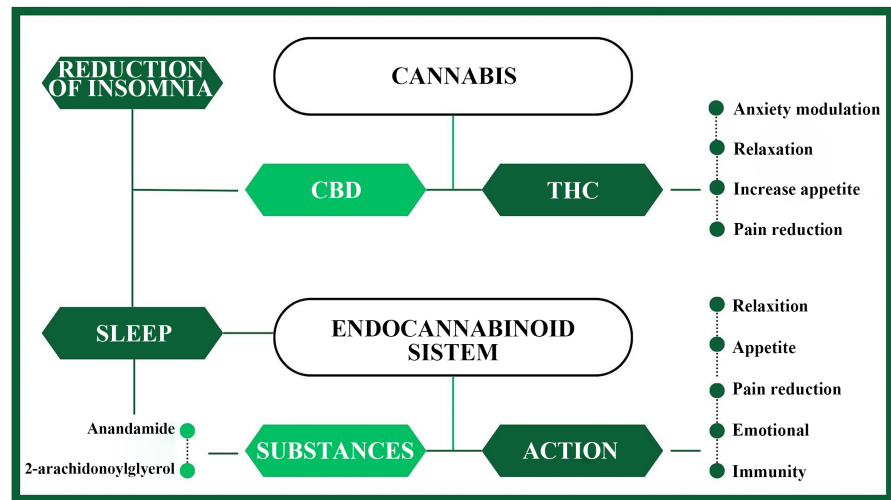


Figure 1. The illustration presents the similarities between THC and CBD (exogenous compounds) and the endocannabinoid system. The focus is on the action of these compounds on sleep and, consequently, on improving insomnia. This effect is represented by the effect of anandamide and CBD on sleep. Thus, the interrelationship between anandamide and CB represents a strong correlation between the exogenous system (cannabis) and the endocannabinoid system, showing that the improvement of insomnia by CBD can be correlated with a system in the human body itself.

The components of this system include cannabinoid receptors 1 (CB1) and 2 (CB2) and their endogenous ligands, including anandamide (AEA) and 2-arachidonoylglycerol (2-AG).

In addition, there is the anandamide transporter (AMT), which plays a fundamental intracellular role in promoting sleep by reuptake of anandamide into the neuronal membrane [20] (Di Marzo, 2004). Anandamide is related to sleep promotion. Its synthesis is increased during non-REM sleep through a molecular pathway that blocks the enzyme that degrades it, fatty acid amide hydrolase FAAH [21]. These findings have already been demonstrated in animal models, through studies with mice that obtained improved sleep without this enzyme [22].

The location of these components in the nervous system can also change depending on the type of insomnia. CB1 and CB2 receptors and their ligands have been identified in the hippocampus, pons, hypothalamus, prefrontal cortex, striatum, nucleus accumbens and cerebrospinal fluid. The hippocampus is known to

be one of the structures with high concentrations of CB1, and in addition to its role in memory, research suggests that the hippocampus is a fundamental site for homeostatic mechanisms during sleep [23]. It is, therefore, essential to consider that studies evaluating sleep should consider volunteers with hippocampus-dependent diseases or disorders, which could lead to biases in the results. Another point we would like to highlight here is that the studies selected for this review do not explain which cellular or molecular mechanisms are modulating these positive responses to insomnia. This way, we understand that modulation of the endocannabinoid system plays a very significant role and could possibly explain these findings.

Another limiting aspect to consider in the studies analyzed is that they do not discuss the homeostatic circadian rhythm in depth. Endocannabinoids have circadian rhythmicity, so they could modulate the sleep-wake cycle. In this sense, the use of cannabinoids could also interfere with this cycle. There are various cellular and molecular mechanisms, as well as neurotropic and biochemical components, that modulate the sleep-wake cycle. In this sense, a deeper understanding of the role of the endocannabinoid system in sleep effectively provides greater insight into the possible interference in insomnia [23].

Another important point to think about is the safety of cannabis compounds, such as CBD and THC, which are targets for insomnia treatment. To date, the articles consider the use of CBD to be safe [24], as no cases of overdose by cannabinoids have been reported. In relation to THC, the articles on the treatment of insomnia using cannabis show an improvement in the symptoms of insomnia, such as a reduction in nocturnal awakenings and in the sleep onset time [17].

On the other hand, one point to be discussed here is the route of administration. The treatments proposed by researchers on the subject used cannabis active ingredients in the form of medicinal oil, sublingual tablets, and even smoking. Each one showed improvement in some of the symptoms presented by patients with insomnia, but of these, the one that showed the greatest results was the sublingual cannabinoid method, called ZTL-101 [12]. Even so, to determine the relevance of the treatment, more important than the form in which the active ingredient was used (medicinal oil, sublingual tablet, and smoking) was the way in which the treatment was conducted, i.e., the studies that showed greater control and definition in the dosage and timing of the treatment can be considered the safest and most beneficial.

However, currently, there are still few studies on the clinical relevance of cannabis in the treatment of insomnia. It is therefore hoped that in the future, more studies will be carried out on the subject, especially in relation to the endocannabinoid system, as discussed here, to better understand the cellular and molecular mechanisms of this sleep disorder.

This way, it will be possible to define how beneficial the use of cannabis is in relation to insomnia, and, if they conclude that this treatment is indeed beneficial, it will lead to patients diagnosed with insomnia having a better quality of sleep and life through the medicinal use of cannabis compounds.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Bollu, P.C. and Kaur, H. (2019) Sleep Medicine: Insomnia and Sleep. *Journal of the Missouri State Medical Association*, **116**, 68-75.
- [2] Martinez, D., Lenz, M.D.C.S. and Menna-Barreto, L. (2008) Diagnóstico dos transtornos do sono relacionados ao ritmo circadiano. *Jornal Brasileiro de Pneumologia*, **34**, 173-180. <https://doi.org/10.1590/s1806-37132008000300008>
- [3] Dopheide, J.A. (2020) Insomnia Overview: Epidemiology, Pathophysiology, Diagnosis and Monitoring, and Nonpharmacologic Therapy. *The American Journal of Managed Care*, **26**, S76-S84. <https://doi.org/10.37765/ajmc.2020.42769>
- [4] Roth, T. (2007) Insomnia: Definition, Prevalence, Etiology, and Consequences. *Journal of Clinical Sleep Medicine*, **3**, 7-10. <https://doi.org/10.5664/jcsm.26929>
- [5] Perlis, M.L., Posner, D., Riemann, D., Bastien, C.H., Teel, J. and Thase, M. (2022) Insomnia. *The Lancet*, **400**, 1047-1060. [https://doi.org/10.1016/s0140-6736\(22\)00879-0](https://doi.org/10.1016/s0140-6736(22)00879-0)
- [6] Bastien, C.H. and Cote, K.A. (2021) Insomnia: A Magnifying Glass to Measure Hyperarousal in Rem. *Sleep*, **44**, zsab184. <https://doi.org/10.1093/sleep/zsab184>
- [7] Morin, C.M. and Jarrin, D.C. (2022) Epidemiology of Insomnia: Prevalence, Course, Risk Factors, and Public Health Burden. *Sleep Medicine Clinics*, **17**, 173-191. <https://doi.org/10.1016/j.jsmc.2022.03.003>
- [8] Walsh, J.H., Maddison, K.J., Rankin, T., Murray, K., McArdle, N., Ree, M.J., *et al.* (2021) Treating Insomnia Symptoms with Medicinal Cannabis: A Randomized, Crossover Trial of the Efficacy of a Cannabinoid Medicine Compared with Placebo. *Sleep*, **44**, zsab149. <https://doi.org/10.1093/sleep/zsab149>
- [9] Crocq, M. (2020) History of Cannabis and the Endocannabinoid System. *Dialogues in Clinical Neuroscience*, **22**, 223-228. <https://doi.org/10.31887/dcns.2020.22.3/mcrocq>
- [10] Shannon, S., Lewis, N., Lee, H. and Hughes, S. (2019) Cannabidiol in Anxiety and Sleep: A Large Case Series. *The Permanente Journal*, **23**, 18-041. <https://doi.org/10.7812/tpp/18-041>
- [11] Lu, H. and Mackie, K. (2021) Review of the Endocannabinoid System. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, **6**, 607-615. <https://doi.org/10.1016/j.bpsc.2020.07.016>
- [12] Gilman, J.M., Schuster, R.M., Potter, K.W., Schmitt, W., Wheeler, G., Pachas, G.N., *et al.* (2022) Effect of Medical Marijuana Card Ownership on Pain, Insomnia, and Affective Disorder Symptoms in Adults. *JAMA Network Open*, **5**, e222106. <https://doi.org/10.1001/jamanetworkopen.2022.2106>
- [13] Ried, K., Tamanna, T., Matthews, S. and Sali, A. (2022) Medicinal Cannabis Improves Sleep in Adults with Insomnia: A Randomised Double-Blind Placebo-Controlled Crossover Study. *Journal of Sleep Research*, **32**, e13793. <https://doi.org/10.1111/jsr.13793>
- [14] Miller, M.B., Carpenter, R.W., Freeman, L.K., Curtis, A.F., Yurasek, A.M. and McCrae, C.S. (2022) Cannabis Use as a Moderator of Cognitive Behavioral Therapy for Insomnia. *Journal of Clinical Sleep Medicine*, **18**, 1047-1054. <https://doi.org/10.5664/jcsm.9796>

- [15] Alnawwar, M.A., Alraddadi, M.I., Algethmi, R.A., Salem, G.A., Salem, M.A. and Alharbi, A.A. (2023) The Effect of Physical Activity on Sleep Quality and Sleep Disorder: A Systematic Review. *Cureus*, **15**, e43595. <https://doi.org/10.7759/cureus.43595>
- [16] Drake, C.L., Kalmbach, D.A., Arnedt, J.T., Cheng, P., Tonnu, C.V., Cuamatzi-Castellan, A., *et al.* (2018) Treating Chronic Insomnia in Postmenopausal Women: A Randomized Clinical Trial Comparing Cognitive-Behavioral Therapy for Insomnia, Sleep Restriction Therapy, and Sleep Hygiene Education. *Sleep*, **42**, zsy217. <https://doi.org/10.1093/sleep/zsy217>
- [17] Vaillancourt, R., Gallagher, S., Cameron, J.D. and Dhalla, R. (2022) Cannabis Use in Patients with Insomnia and Sleep Disorders: Retrospective Chart Review. *Canadian Pharmacists Journal/Revue des Pharmaciens du Canada*, **155**, 175-180. <https://doi.org/10.1177/17151635221089617>
- [18] Lavender, I., McGregor, I.S., Suraev, A., Grunstein, R.R. and Hoyos, C.M. (2022) Cannabinoids, Insomnia, and Other Sleep Disorders. *Chest*, **162**, 452-465. <https://doi.org/10.1016/j.chest.2022.04.151>
- [19] Dasram, M.H., Walker, R.B. and Khamanga, S.M. (2022) Recent Advances in Endocannabinoid System Targeting for Improved Specificity: Strategic Approaches to Targeted Drug Delivery. *International Journal of Molecular Sciences*, **23**, Article 13223. <https://doi.org/10.3390/ijms232113223>
- [20] Marzo, V.D., Bifulco, M. and Petrocellis, L.D. (2004) The Endocannabinoid System and Its Therapeutic Exploitation. *Nature Reviews Drug Discovery*, **3**, 771-784. <https://doi.org/10.1038/nrd1495>
- [21] D'Souza, D.C., Cortes-Briones, J., Creatura, G., Bluez, G., Thurnauer, H., Deaso, E., *et al.* (2019) Efficacy and Safety of a Fatty Acid Amide Hydrolase Inhibitor (PF-04457845) in the Treatment of Cannabis Withdrawal and Dependence in Men: A Double-Blind, Placebo-Controlled, Parallel Group, Phase 2a Single-Site Randomised Controlled Trial. *The Lancet Psychiatry*, **6**, 35-45. [https://doi.org/10.1016/s2215-0366\(18\)30427-9](https://doi.org/10.1016/s2215-0366(18)30427-9)
- [22] Huitron-Resendiz, S., Sanchez-Alavez, M., Wills, D.N., Cravatt, B.F. and Henriksen, S.J. (2004) Characterization of the Sleep-Wake Patterns in Mice Lacking Fatty Acid Amide Hydrolase. *Sleep*, **27**, 857-865. <https://doi.org/10.1093/sleep/27.5.857>
- [23] Brankač, J., Platt, B. and Riedel, G. (2009) Sleep and Hippocampus: Do We Search for the Right Things? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **33**, 806-812. <https://doi.org/10.1016/j.pnpbp.2009.03.027>
- [24] Ranum, R.M., Whipple, M.O., Croghan, I., Bauer, B., Toussaint, L.L. and Vincent, A. (2022) Use of Cannabidiol in the Management of Insomnia: A Systematic Review. *Cannabis and Cannabinoid Research*, **8**, 213-229. <https://doi.org/10.1089/can.2022.0122>