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Review Article: Sleep, Pain and Cannabis

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Abstract

One of the most common reasons that patients report the use of cannabis for medical purposes is to reduce pain and improve sleep. Despite this repeated association, it is not clear whether the effects of cannabis use on pain are mediated by the effect of improved sleep, or vice versa. This distinction may have important therapeutic implications as different cannabis preparations have different pharmacokinetic properties; short acting cannabinoids may therefore initiate sleep but not maintain it, while longer acting cannabinoids may be better at sleep maintenance than initiation. Recent reviews have examined the quantitative outcomes of sleep measures in clinical trials of cannabinoids in a range of disorders but did not focus on pain; others focused exclusively on one cannabinoid preparation. Given the current interest in the potential therapeutic uses of cannabis, we have prepared a general review of sleep, pain and cannabis with a view to identifying gaps in our knowledge that could be addressed in further research.

Keywords: Cannabis; Marijuana; Sleep; Pain

Introduction

One of the most common reasons that patients report the use of cannabis for medical purposes is to reduce pain and improve sleep. Despite this repeated association, it is not clear whether the effects of cannabis use on pain are mediated by the effect of improved sleep, or vice versa. This distinction may have important therapeutic implications as different cannabis preparations have different pharmacokinetic properties; short acting cannabinoids may therefore initiate sleep but not maintain it, while longer acting cannabinoids may be better at sleep maintenance than initiation.

Recent reviews have examined the quantitative outcomes of sleep measures in clinical trials of cannabinoids in a range of disorders [1] but did not focus on pain; others focused exclusively on one cannabinoid preparation [2]. Given the current interest in the potential therapeutic uses of cannabis, we have prepared a general review of sleep, pain and cannabis with a view to identifying gaps in our knowledge that could be addressed in further research.

Cannabinoids: A Primer

Historical evidence suggests that the plant Cannabis sativa has been used for millennia for the treatment of pain and nausea [3]. In cannabis, over 100 cannabinoids (defined as the terpenophenolic compounds found in Cannabis sativa) have been identified, of which the most well-studied are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The physiological effects of cannabinoids are well described and affect learning and memory, appetite, pain, mood, sleep, movement, reward pathways, as well as effects on the immune system [4,5]. Interestingly, the pharmacological effects of THC appear to be biphasic whereby effects at low doses are different from those at high doses [5].

Two major endogenous cannabinoids have been described: anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). These lipid molecules are synthesized on demand from post-synaptic neurons and bind to G protein-coupled cannabinoid receptors (GPCR) CB1 (located on presynaptic nerve terminals) and CB2 (located on immune cells including microglia and macrophages) [5]. The CB1 receptor is found in the brain regions that have to do with motor control, cognition, emotional responses, motivated behavior, and homeostasis [6]. In humans, the CB1 receptor is found in high density in the central nervous system (CNS) in areas such as the thalamus, hypothalamus, hippocampus, cortex, limbic system, and the basal ganglia [7] (Figure 1).

The role of the CB2 receptor is not as well characterized as the CB1 receptor, but it is believed to have a role in modulation of immune function. CB2 receptors are located in the thymus, lungs, testicles, and spleen and absent from the brain, heart, kidney, and liver [8]. However more recently CB2 receptors were found in the brainstem [9] and their role in neuroinflammation is receiving increased attention [10].

THC acts on CB1 and, to a lesser extent, CB2 receptors and is psychoactive [4]. CBD is non-psychotropic and has a very low affinity for the CB1 and CB2 receptors; CBD has even been found to antagonize CB1 agonists. CBD is currently being examined for suppression of inflammation promoting cytokines in rheumatoid arthritis, and type 1 diabetes, protection against acute and chronic neurodegeneration, anxiety, and cancer. It also has antiemetic and anti-nausea properties [11]. When THC is given to healthy volunteers as a single agent before sleep, overnight memory is impaired in the morning but if equal parts THC: CBD are given there appears to be no memory impairment [12], suggesting that ratios of THC and CBD are important in adverse event profiles.

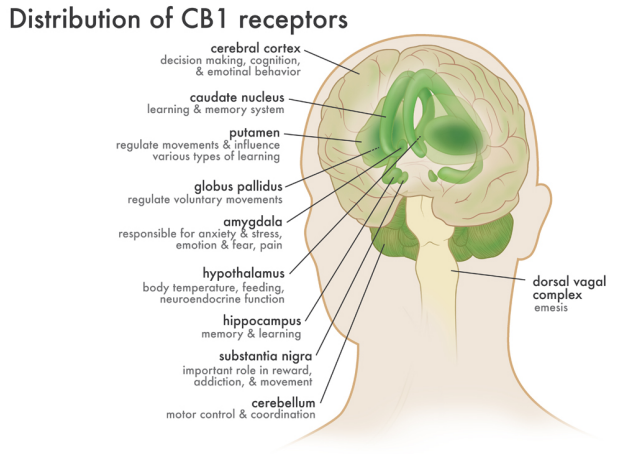

Figure 1: Image courtesy of the Canadian Consortium for the Investigation of Cannabinoids.

Sleep and Pain

Pain is the most common reason for people to seek medical attention, and sleep problems are among the most frequent complaints of acute and chronic pain sufferers. The combined influence of pain and poor sleep can have profound effects on the biological and behavioral state of an individual [13]. Lack of slow wave sleep (SWS) and rapid eye movements (REM) caused by acute or chronic pain has been shown to increase the perception of pain, and recovery from SWS deprivation has a significantly greater analgesic effect than does REM recovery [14].

Pain and sensation are drastically reduced during REM and non-REM sleep [15]. The pathways responsible for this remain poorly understood. Pain is relayed through ascending pathways from the body (spinothalamic tract) and face (trigemino-thalamic tract) to higher cortical areas in the brain [16]. Pain manifests itself in sleep by delaying the onset and fragmenting sleep [17].

Chronic pain patients have a reduction in SWS and poor overall sleep efficiency brought on by microarousals and shifts in sleep stages i.e. sleep fragmentation [18,19]. Ohayon et al. [20] found that 23% of chronic pain sufferers (>= 6 months in duration) had at least one symptom of insomnia and 40.2% of subjects with insomnia symptoms had at least one type of chronic pain. This study however needs to be interpreted cautiously as subjects were not screened for preexisting conditions such as depression which is known to affect sleep. The relationship between pain and sleep may be reciprocal: pain disrupts sleep which in turn exacerbates pain [19].

Monitoring acute pain responses during sleep has shown that noxious intramuscular stimuli force the subject awake regardless of sleep stage, but non-noxious stimuli only causes microarousals [21].

Another study of acute post-operative pain found that total sleep was decreased for 1 to 2 nights and that sleep was fragmented. For the first 2 nights after surgery REM sleep was absent but was made up for on subsequent nights. SWS duration was reduced for up to 4 nights. This study however had many variables as it may not have just been pain that caused the change in sleep but also the hospital environment, stress from surgery and the analgesic medication the patients were administered [13].

Other Conditions Involving Sleep and Pain

There are several well-described conditions which highlight the important interaction between pain and sleep.

Restless leg syndrome

Restless leg syndrome (RLS) is a neurological disorder in which vague painful sensations in the legs occur during periods of muscular inactivity. Pain appears with a circadian rhythm, peaking between midnight and 4:00 am, causing sufferers to be unable to get to sleep [22]. RLS is associated with an increased risk of depression and anxiety [23]; lack of sleep due to RLS contributes to the increase the risk of depressive disorders, and sleep deprivation has been known to exacerbate panic attacks and can even precipitate them in certain individuals [24].

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is defined as a pattern of interrupted breathing during sleep which also causes fractured sleep. Patients with OSA wake up frequently during the night due to lack of oxygen intake caused by the collapse of the upper airway. This causes them to be constantly tired since they are rarely getting to SWS and spend less time in REM sleep [25]. Subjects with major depression are five times more likely to have a sleep related breathing disorder than non-depressive subjects [26]. OSA has been documented in studies of chronic pain patients with disorders such as rheumatoid arthritis and fibromyalgia. Studies of patients with symptoms of fibromyalgia have led some investigators to propose that certain individuals may instead have a sleep apnea syndrome and the medications prescribed for fibromyalgia would actually worsen the sleep apnea symptoms [27]. OSA is more prevalent in chronic pain patients who use opioid-based drugs for pain management compared to the general population [28]. Sleep apnea is also frequently linked to headaches [27].

Cannabinoids and Sleep

Clinical cannabis research is predominantly focused on symptom management using compounds derived from cannabis called cannabinoids, and it has been suggested that one of the additional benefits of cannabinoid use is increasing sleep quality. Indeed one of the main reasons that patients report using herbal cannabis is to improve sleep quality [29]. Given our improved understanding of the endocannabinoid system (ECS), It is worth exploring the underlying rationale for this effect.

Anatomical data suggests that the CB1 receptor may be involved in the modulation of sleep [7]. Research on cannabis and THC extract from the 1970s and 1980s showed that cannabinoids have an effect on sleep by increasing SWS and decreasing REM sleep, but these studies were poorly controlled. The earliest reported studies of the primary psychoactive cannabinoid delta-9-tetrahydrocannabinol (THC) on sleep explored the hypnotic effects of different dose levels of THC [30]; the effect of the isomer delta-8-THC on EEG activity and sleep was explored in cats [31] and rats [32].

In a single dose human study examining cannabinoid effects on sleep, administration of CBD alone increased wakefulness, while THC was found to have no adverse effect on sleep and in some individuals

increased the amount of SWS. The effect of equal parts THC and CBD was found to decrease stage 3 sleep, but had no effect on the duration of stage 2 or SWS [12]. This suggests that THC may acts as a sedative whereas CBD as a stimulant.

The physiological role of endocannabinoids on sleep has been explored. Intracerebroventricular injection of AEA enhances SWS and REM sleep through actions at the CB1 receptor [7]. The effect of AEA effect was enhanced when injected into the pedunculopontine tegmental nucleus. It was hypothesized that AEA, acting through CB1, induces an increase in the activity of the cholinergic neurons of the brainstem and basal forebrain that are involved in inducing sleep.

Cannabis and Sleep: Clinical Evidence

It is important to recognize that the effects of cannabis on sleep have been examined in recreational users as well as patients. Among heavy cannabis users, shorter REM latency and a longer sleep onset have been observed compared to controls [33]. Cessation of long-term heavy use of cannabis reduces sleep quality by decreasing total sleep length as well as the amount of SWS [34]. Poor sleep quality was one of the reasons that abstinent heavy cannabis users relapse [35].

Among patients with chronic pain, early experience with the synthetic cannabinoid nabilone found that one of the main reasons nabilone was continuously used was due to improvement in sleep quality [36]. Other observational studies have found that smoked cannabis is used by patients with chronic non-cancer pain to help decrease their pain and improve sleep [37]. Cannabis use in patients with post-traumatic stress disorder has also been reported to increase sleep quality [38].

Clinical trials with synthetic cannabinoids have shown some promise for dealing with sleep and pain. A study by Notcutt et al. [39] on chronic pain found that THC and THC: CBD reduced pain scores in patients but had little to no effect on the duration of sleep, while the perceived quality of sleep increased dramatically. Nabiximols, an oromucosal drug containing a 1:1 ration of THC: CBD drug has been tested for its effectiveness on pain and sleep interactions in several pain conditions including multiple sclerosis (MS) [2]. Nabiximols has been shown to reduce insomnia and daytime fatigue and to improve sleep quality in both MS and neuropathic pain patients. In the patients in whom it was beneficial, no evidence of tolerance or cognitive problems was noted [2]. Rog et al. [40] performed a randomized, control trial on cannabis-based medicine in central pain in MS patients. They found that nabiximols was effective in reducing pain and pain-related sleep disturbances. Nabiximols was also tried on patients with rheumatoid arthritis and was found significantly reduce pain on movement, pain and rest and the quality of sleep [41].

A study done by Ware et al. [42] on fibromyalgia (FM) patients tested the efficacy of another synthetic cannabinoid, nabilone, which mimics the action of THC. FM-related insomnia is usually treated with low-dose tricyclic antidepressants such as amitriptyline. However, nabilone was found to be superior to amitriptyline in improving the sleep quality of FM patients while the effects on pain, mood and quality of life were similar. Drowsiness and dizziness were common adverse events but these were similar to the side effects of amitriptyline.

Dronabinol, a synthetic version of THC, has been found to be useful for nighttime agitation related to severe dementia. Nighttime motor activity was found to decrease in dementia sufferers after the first dose of dronabinol, and while the mechanism of action is not clear, it may be due to sleep induction. Dronabinol was found to have dose dependent side effects and other studies showed effects on the cognition and function of patients but this was not examined in this study [43]. Dronabinol has also demonstrated effectiveness in treating central pain due to MS [44,45]. Intriguingly, THC has been found to stabilize respiratory patterns during all sleep stages and reducing sleep apnea in a dose dependent fashion [46].

A systematic review of cannabinoids and sleep completed in 2013, which addresses many of the articles presented above, points to the fact that many of the studies have bias and were not properly controlled. Despite the poor studies the authors of the review state that cannabinoids may play a role in sleep most specifically when pain is involved but the current evidence was not sufficient enough to say for certain [1].

What Needs to be Studied?

Sleep is a complex and poorly understood phenomenon integral to quality of life. Cannabinoids appear to have a potential role in improving perceived sleep quality, but overall there is very little data on the effects of cannabinoids on sleep architecture. It will be important to demonstrate the long term effects of cannabis and cannabinoid-based medicines, like nabilone and nabiximols, as well as medical cannabis on sleep. They should be validated by further randomized clinical trials and long term surveillance studies [37]. In-depth studies using polysomnography will be needed to understand to a greater extent the effects of cannabinoids on sleep architecture and the relationship of such changes to the patient's perceived quality of sleep [2]. A key question is whether the cannabinoid helps pain and therefore sleep is a secondary effect, or whether they affect sleep primarily and the pain relief is a function of a better rested state and therefore better coping skills.

Cannabinoid medications have typically been used as a last resort for chronic pain patients when other conventional methods have failed. These cases are often very complex and are hard to study since the chronic pain is heterogeneous with variable pathophysiological mechanisms [39]. For many patients with chronic pain, obtaining a good night's sleep can be a huge milestone and an important objective in setting treatment outcomes.

Emerging neurobiological findings show that the ECS system may be involved in areas of the brain associated with depression but further conclusive research is needed [47]. Animal depression studies point to doses of THC 2.5 mg/kg, CBD 200 mg/kg, and cannabichromene (CBC) 20 mg/kg acting as an antidepressant in some animal models. However to date, no clinical trials have been undertaken to test cannabinoids on affective disorders [48]. Due to the link between insomnia and depression, this may give interesting insights into the effect cannabinoids have in depression/insomnia/pain interactions and may help clinicians better understand the potential roles of cannabinoid based medicines, particularly in disorders like fibromyalgia where sleep disturbances, depression, and pain all coexist [42]. Polysomnographic studies of FM patients have shown that sleep architecture is disordered causing a delay in the onset of sleep, poorer sleep efficiency and reduced SWS and REM sleep. Various other non-REM sleep physiology alterations have been found [49]. Studies using polysomnography of FM patients and others using cannabinoid medicines are needed to verify the effect of cannabinoids on sleep architecture in such conditions.

References

1. Gates PJ, Albertella L, Copeland J (2014) The effects of cannabinoid administration on sleep: a systematic review of human studies. Sleep Med Rev 18: 477-487.
2. Russo EB, Guy GW, Robson PJ (2007) Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. Chem Biodivers 4: 1729-1743.
3. Russo E (1998) Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. Pain 76: 3-8.
4. Iversen L (2003) Cannabis and the brain. Brain 126: 1252-1270.
5. Mechoulam R and LA Parker (2012) The Endocannabinoid System and the Brain. Annu Rev Psychol.
6. Rodríguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, et al. (2005) The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol 40: 2-14.
7. Murillo-Rodríguez E (2008) The role of the CB1 receptor in the regulation of sleep. Prog Neuropsychopharmacol Biol Psychiatry 32: 1420-1427.
8. Brown SM, Wager-Miller J, Mackie K (2002) Cloning and molecular characterization of the rat CB2 cannabinoid receptor. Biochim Biophys Acta 1576: 255-264.
9. Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, et al. (2005) Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 310: 329-332.
10. Rom S, Persidsky Y (2013) Cannabinoid receptor 2: potential role in immunomodulation and neuroinflammation. J Neuroimmune Pharmacol 8: 608-620.
11. Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO (2007) Cannabidiol--recent advances. Chem Biodivers 4: 1678-1692.
12. Nicholson AN, Turner C, Stone BM, Robson PJ (2004) Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J Clin Psychopharmacol 24: 305-313.
13. Roehrs T, Roth T (2005) Sleep and pain: interaction of two vital functions. Semin Neurol 25: 106-116.
14. Onen SH, Alloui A, Gross A, Eschallier A, Dubray C (2001) The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. J Sleep Res 10: 35-42.
15. Lavigne G, Zucconi M, Castronovo C, Manzini C, Marchettini P, et al. (2000) Sleep arousal response to experimental thermal stimulation during sleep in human subjects free of pain and sleep problems. Pain 84: 283-290.
16. Willis WD, Westlund KN (1997) Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol 14: 2-31.
17. Harding SM (1998) Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci 315: 367-376.
18. Lavigne McMillan GD, Zucconi M eds. Principles and Practice of Sleep Medicine. Principles and Practice of Sleep Medicine, ed. Kryger M, Roth T, and Demeent W. 2005 Elsevier; Philidelphia: 1246-1255.
19. Smith MT, Haythornthwaite JA (2004) How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Med Rev 8: 119-132.
20. Ohayon MM (2005) Relationship between chronic painful physical condition and insomnia. J Psychiatr Res 39: 151-159.
21. Lavigne G, Brousseau M, Kato T, Mayer P, Manzini C, et al. (2004) Experimental pain perception remains equally active over all sleep stages. Pain 110: 646-655.
22. Michaud M, Dumont M, Selmaoui B, Paquet J, Fantini ML, et al. (2004) Circadian rhythm of restless legs syndrome: relationship with biological markers. Ann Neurol 55: 372-380.
23. Earley CJ (2003) Clinical practice. Restless legs syndrome. N Engl J Med 348: 2103-2109.
24. Winkelmann J, Prager M, Lieb R, Pfister H, Spiegel B, et al. (2005) "Anxietas tibiarum". Depression and anxiety disorders in patients with restless legs syndrome. J Neurol 252: 67-71.
25. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, et al. (2009) Marked reduction in obstructive sleep apnea severity in slow wave sleep. J Clin Sleep Med 5: 519-524.
26. Ohayon MM (2003) The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry 64: 1195-1200.
27. Menefee LA, Cohen MJ, Anderson WR, Doghramji K, Frank ED, et al. (2000) Sleep disturbance and nonmalignant chronic pain: a comprehensive review of the literature. Pain Med 1: 156-172.
28. Webster LR, Choi Y, Desai H, Webster L, Grant BJ (2008) Sleep-disordered breathing and chronic opioid therapy. Pain Med 9: 425-432.
29. Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, et al. (2013) Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. Int J Drug Policy 24: 511-516.
30. Cousens K, DiMascio A (1973) (-) Delta 9 THC as an hypnotic. An experimental study of three dose levels. Psychopharmacologia 33: 355-364.
31. Wallach MB, Gershon S (1973) The effects of delta8-THC on the EEG, reticular multiple unit activity and sleep of cats. Eur J Pharmacol 24: 172-178.
32. Friedman E, Gershon S (1974) Effect of delta8-THC on alcohol-induced sleeping time in the rat. Psychopharmacologia 39: 193-198.
33. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, et al. (2008) Sleep disturbance in heavy marijuana users. Sleep 31: 901-908.
34. Vandrey R, Smith MT, McCann UD, Budney AJ, Curran EM (2011) Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. Drug Alcohol Depend 117: 38-44.
35. Babson KA, Boden MT, Harris AH, Stickle TR, Bonn-Miller MO (2013) Poor sleep quality as a risk factor for lapse following a cannabis quit attempt. J Subst Abuse Treat 44: 438-443.
36. Berlach DM, Shir Y, Ware MA (2006) Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med 7: 25-29.
37. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ (2003) Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain 102: 211-216.
38. Bonn-Miller MO, Babson KA, Vandrey R (2014) Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD. Drug Alcohol Depend 136: 162-165.
39. Notcutt W, Price M, Miller R, Newport S, Phillips C, et al. (2004) Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia 59: 440-452.
40. Rog DJ, Nurmikko TJ, Friede T, Young CA (2005) Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 65: 812-819.
41. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS (2006) Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 45: 50-52.
42. Ware MA, Fitzcharles MA, Joseph L, Shir Y (2010) The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg 110: 604-610.
43. Walther S, Mahlberg R, Eichmann U, Kunz D (2006) Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. Psychopharmacology (Berl) 185: 524-528.
44. Svendsen KB, Jensen TS, Bach FW (2004) Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 329: 253.
45. Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA, et al. (2001) Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 323: 13-16.
46. Carley DW, Paviovic S, Janelidze M, Radulovacki M (2002) Functional role for cannabinoids in respiratory stability during sleep. Sleep 25: 391-398.
47. Vinod KY, Hungund BL (2006) Role of the endocannabinoid system in depression and suicide. Trends Pharmacol Sci 27: 539-545.

48. Serra G, Fratta W (2007) A possible role for the endocannabinoid system in the neurobiology of depression. Clin Pract Epidemiol Ment Health 3: 25.

49. Spaeth M, Rizzi M, Sarzi-Puttini P (2011) Fibromyalgia and sleep. Best Pract Res Clin Rheumatol 25: 227-239.