Understanding the Evidence for Medical Cannabinoids for the Treatment of Chronic Pain

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ABSTRACT

This paper is an examination of the existing literature on the use of medical cannabinoids for the treatment of adults with chronic pain (CP). The use of medical cannabinoids in the treatment of CP has been a controversial topic due to societal associations with the recreational use of cannabis and the lack of information as to their analgesic effects. This paper analyzes trends in how medical cannabinoids perform as an analgesic treatment for adults with CP, especially in comparison to opioids. Additionally, this paper explores any secondary effects participants may experience as a result of treatment with medical cannabinoids. It will be shown that, while medical cannabinoids have the potential to reduce pain in those suffering from CP, there are numerous factors that must be considered before they become an acceptable treatment option. In addition, there is evidence that the analgesic effects of medical cannabinoids may be primarily due to their intoxicating effect rather than their interaction with neural pain pathways. This review of existing literature acts to guide future research on the use of medical cannabinoids for the treatment of CP.

Introduction

Patients with chronic pain (CP) often describe their everyday bodily sensations as a knife being stabbed into the back, a bad sunburn that won't go away, metal filings under the skin, an open wound, or an electric shock. CP is the debilitating side-effect of numerous diseases and conditions, including cancer[1], peripheral neuropathy[2-4,12-14], and fibromyalgia[3-5]. CP affects more than 1.5 billion people around the world[6] and 64% of American adults over the age of 30[7]. It is characterized by ongoing pain lasting longer than 3 months[7] that is often comorbid with sleep[3,5-7] and mood disturbances[3,6,7]. Current treatment is largely reliant on opioids, which have a high potential for abuse[6] and often leave patients still in pain[3]. Considering the current opioid epidemic, an alternative treatment option for individuals with uncontrolled CP is needed, as physicians begin to limit the duration and dosage of opioid prescriptions[11].

Medical cannabinoids have shown to have some analgesic effects[2-5,8,13,14] and the potential to help individuals with CP reduce their opioid intake[9,11]. However, cannabis's history as a recreational drug has led to concerns about its efficacy and safety from physicians, patients, and the public, making its implementation as an established treatment option slow. The purpose of this review paper is to analyze medical cannabinoids in the treatment of adults with CP, specifically its effectiveness in pain-relief, emotional outcomes, and safety. This review will shed light on the gaps in knowledge that exist in the current evidence for treatment and make recommendations for future research.

Background

The cannabis plant (*Cannabis sativa*) contains hundreds of cannabinoids that interact with CB_1 receptors in the central nervous system[5,13,14] and CB_2 receptors on immune cells throughout the body[5,13]. The major cannabinoid is Δ^9-tetrahydrocannabinol (THC), which is responsible for the "drug high" associated with cannabis use[5]. According to

Weizman et al.[2], THC's interaction with the anterior cingulate cortex (ACC) in the brain may account for its analgesic effects. Cannabidiol (CBD) is another major component of cannabis that affects mood and cognition but does not produce intoxicating effects[5]. The interplay of these two components, the ratio of THC to CBD, and the method of administration are all extremely important in determining whether patients experience any pain-relieving effects.

Analgesic Effects

In the majority of the clinical trials analyzed here, significant positive results were found for the analgesic efficacy of medical cannabinoids. These results, however, are dependent on numerous factors, creating an extremely complex, interconnected body of evidence that is difficult to untangle in terms of creating a standard dose, THC to CBD ratio, or method of administration for specific diseases or conditions characterized by CP. There are some patterns in the evidence that have been evaluated here, but more research on the analgesic effects of medical cannabinoids needs to be conducted in order to separate these influences.

Methods of Administration

Medical cannabinoids may be delivered to the body in numerous ways. Often, the cannabis plant material is smoked, either in a cannabis cigarette[11,15] or by using a vaporizer[5,13,14]. In controlled studies, the Volcano® Medic Vaporizer is a common delivery system in which the plant material is heated to convert the THC and CBD acids into vapor[5,13,14]. This vapor is contained within a plastic balloon, allowing patients to inhale controlled amounts for specific intervals[5,13,14]. The dried flower tops of the cannabis plant may also be made into a decoction by boiling it in water and milk[3]. Another option is a nabiximols oromucosal spray (Sativex®) that is administered orally[1]. Additionally, CBD and THC oils may be absorbed sublingually (under the tongue)[2] or put into food items and absorbed in the digestive track. Oral tablets, such as Namisol®[10] or dronabinol[12] are other options.

Success was seen in studies in which the cannabis plant was smoked, made into a decoction, or absorbed sublingually in its oil form. Nonsignificant results were seen when THC was administered via an oral tablet. Namisol® tablets with standardized THC content did not produce statistically different results from placebo on any of the measures of pain or secondary outcomes in patients with chronic abdominal pain[10]. Similarly, another study using a synthetic form of THC called dronabinol[12] found no significant differences between treatment and control conditions in neuropathic pain patients[12]. These results indicate that, when taken orally, THC may have a reduced analgesic effect. This may be due to decreased absorption in the digestive track, compared to intrapulmonary or sublingual absorption.

THC to CBD Ratios

The vast majority of the clinical trials being analyzed used medical cannabinoids with high THC ratios. In general, higher THC ratios were associated with increased significant results[2,3,5,8,11,13,14]. In a 2019 study by van de Donk et al.[5], four different varieties of cannabis (Bedrocan® with high THC/low CBD; Bediol® with high THC/high CBD; Bedrolite® with low THC/high CBD; and a placebo variety without any THC or CBD) with standardized THC and CBD concentrations were compared for their analgesic effects in patients with CP due to fibromyalgia. Both high THC varieties, Bedrocan® and Bediol®, significantly increased pressure pain tolerance[5], while low THC varieties were not significant on any measure of pain[5]. This suggests that the level of pain relief may be due to the level of intoxication from THC, instead of interaction in neural pain pathways.

Two similar studies were independently conducted on the analgesic effects of vaporized cannabis of varying THC concentrations in patients with neuropathic pain[13,14]. In the 2016 study by Wilsey et al.[13], cannabis plant material with all the THC extracted (placebo), 2.9% THC content, and 6.7% THC content were compared. The results displayed

a stairstep effect in which pain intensity was highest with the placebo, significantly less with the 2.9% THC dose, and less at the 6.7% THC dose[13]. The two active doses were not significantly different from one another. In the 2015 study by Wallace et al.[14], placebo cannabis plant material was compared against low (1% THC), medium (4% THC), and high (7% THC) doses of cannabis. In all of the varieties, CBD concentration was negligible[14]. The average pain intensity with the placebo was higher, but not statistically different, compared to the low and medium doses[14]. However, the average pain score with the high dose was significantly lower than the placebo[14]. Both of these studies support the findings of van de Donk et al.[5], in which high THC concentrations are associated with greater pain relief.

The reason for the direct relationship between THC content and analgesia may be due in part to its psychoactive effects, but there is also evidence of a neurological interaction. In a 2018 study by Weizman et al.[2], chronic lumbar radicular pain patients received THC oil or placebo oil and then underwent an fMRI scan. Along with finding significant analgesic results for THC compared with placebo[2], the extent of pain relief was correlated with a reduction in the functional connectivity of the anterior cingulate cortex (ACC) and sensorimotor cortex[2]. The authors concluded that THC may disrupt the way these two pain processing pathways interact, reducing the subjective experience of pain[2]. This provides evidence that THC works in reducing pain on both the emotional and biological level.

In trials where a high THC concentration was not used, the results were likely to be nonsignificant. One study used Sativex®, which is has equal concentrations of THC and CBD[1], and the patients experienced slight improvement in average pain and worst pain scores compared to placebo, but this difference was not significant[1].

Disease or Condition Characterized by Chronic Pain

CP presents itself differently in every individual, with the disease or condition it is associated with being a major factor in explaining the specific pain experience of the patient. Medical cannabinoids have been shown to be especially effective in treating diabetic[14], spinal cord-related[13], and radicular[2] neuropathic pain as well as general non-cancer pain[3,8]. In individuals with advanced cancer[1], chronic abdominal pain[10], and multiple sclerosis-related neuropathic pain[12], medical cannabinoids were ineffective in significantly reducing pain. However, nonsignificant results should also be considered in light of the method of administration used. For example, in a study of chronic abdominal pain patients, they were administered Namisol® tablets[10], which were unlikely to be maximally absorbed due to additional gastrointestinal deficits[10]. In this way, the disease or condition may warrant specific methods of administration to achieve optimal absorption of the drug.

Another factor to consider is the way in which pain levels are operationalized. Often, pain is quantified in a self-reported score using a Numerical Rating Scale (NRS)[1,12,13] or Visual Analogue Scale (VAS)[2,3,5,10,13,14]. The NRS is an 11-point numerical scale in which patients rate their pain from 0 (no pain at all) to 10 (worst possible pain)[13]. The VAS presents patients with a horizontal line ranging from no pain on the left to severe pain on the right, representing the spectrum of their pain intensity[14]. Patients indicate their pain by marking a point on the line and their score is determined by measuring the distance between the “no pain” end and their mark[14].

Some studies used these scales to measure specific aspects of pain[5], while others only measured average pain intensity scores[1-3,8,10-15]. This is an important distinction, since the previously mentioned study by van de Donk et al.[5] found an interaction between the type of pain and pain relief in individuals with fibromyalgia. They measured spontaneous pain, pressure pain, and electrical pain, with significant pain relief compared to placebo only in the pressure pain test[5]. However, individuals with fibromyalgia experience symptoms reflective of pressure pain more than electrical pain[5], so these results are useful in as a treatment option for those with this condition. Had the authors only collected average pain scores, significant results may have not presented. This shows the importance of also considering the measures and pain tests used when analyzing a study’s results.

Concurrent Opioid Use

The potential for medical cannabinoids to be used as an adjunctive treatment with prescription opioids is an option that may benefit those who have developed a tolerance or dependence to opioids. In addition, CP patients may still desire to reduce the adverse effects associated with opioid use, such as constipation[11] and respiratory depression[11]. In a 2018 study by Cooper et al.[11], a placebo capsule or oxycodone capsule (2.5 mg or 5.0 mg) was given to healthy, cannabis-experienced participants. After 45 minutes, placebo cannabis or 5.6% THC content cannabis was smoked[11]. The results indicated that on their own, both the active cannabis and the low (2.5 mg) dose of oxycodone did not produce significant effects[11]. However, when the active cannabis was combined with the lose dose of oxycodone, pain was significantly reduced[11]. This provides evidence for the efficacy of cannabis in producing opioid-sparing effects.

Unfortunately, randomized control trials have rigorous exclusion criteria that leave out a significant portion of the CP population that have comorbid mental health disorders or substance abuse disorders[4]. To investigate this gap, Sohler, et al.[9] analyzed the use of cigarettes, alcohol, and illicit drugs among HIV-infected individuals with CP who were prescribed opioids. Cannabis was found to be the most commonly used illicit drug[9], and there was a significant association between cannabis use and abstaining from prescription opioid use[9]. One explanation given by the authors was that those who used cannabis did not also take prescription opioids because the cannabis alone was sufficient for pain management[9]. It is also possible to conclude that individuals may choose to not take prescribed opioids in order to avoid their aversive effects. This study is interesting for its ecological validity and specific focus on high-risk CP patients. It shows how "real" people create their own pain management schedule based on what they prefer and what makes them feel the most comfortable when given multiple analgesic options.

Secondary Effects

Individuals with CP often experience disturbances in their sleep[3,5-7], mood[3,6,7], and productivity[3,6,7]. Sleep disturbance is 2 to 5 times more common in people with CP[6] and 25-40% have major depression[6]. In terms of productivity, $560-635 billion are lost each year[6,7] in the United States due to CP-related medical and economic costs[7]. These additional side effects are not treated by conventional treatment options such as opioids; however, medical cannabinoids may alleviate some of these stressors. Medical cannabinoids tend to be well-tolerated[10-15], decrease anxiety[3,8], depression[3,8], and pain disability[3,8], and increase quality of life[8,12] and sleep[1]. These measures tended to be secondary outcomes that are not heavily investigated, but more research should be conducted on the potential psychological benefits.

The safety of medical cannabinoid use, especially over a long period, is a currently relevant topic that both politicians and physicians are at odds over. In a 2015 study by Ware et al.[8], non-serious adverse effects (AEs) and serious adverse effects (SAEs) were reported over the course of 1 year in chronic non-cancer pain patients who were instructed to self-administer herbal cannabis daily. The risk of having at least one SAE or one AE was not significantly different between the cannabis and control groups[8]. However, those in the cannabis group had an increased rate of respiratory AEs after 1 year compared to control[8]. Additional measures of neurocognitive, liver, renal, pulmonary, and endocrine function showed no significant differences after 1 year between the groups[8]. The authors concluded that cannabis may be a safe addition to pain management programs over the long-term, as long as it is carefully monitored[8]. Other, shorter studies support the evidence that cannabis use did not produce clinically relevant changes in vital signs[10,12,13], hematology[10,12], or biochemistry[10,12].

Conclusion

Medical cannabinoids have the potential to substantially improve the lives of billions of people suffering from CP. Unfortunately, the body of evidence is lacking in order to get a cohesive picture of how cannabinoids produce their

analgesic effect, the optimal route of absorption, and what THC and CBD ratios produce maximal pain relief. In addition, more long-term studies are needed in order for physicians to comfortably prescribe this as a safe treatment option for the long-term condition of CP. Bias in participant self-reports, skewed statistical data, and selectively publishing positive results also limit the current evidence. Once these concerns are addressed, medical cannabinoids may offer CP patients not only pain relief, but emotional and functional support as well.

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