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Cannabinoids and Their Use for Chronic Pain – Cannabinoids as an Alternative to Opioids for Chronic Pain

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Abstract

Study aim: To determine if the literature supports cannabinoids as an alternative treatment to chronic pain. *Background*: Chronic pain is a disabling, expensive, and prevalent condition. As one of the leading causes of disability worldwide, the burden on the healthcare system is high. Management normally includes opioids, which come with many risks for the patient. Cannabis, a more recent development in pain management, potentially mitigates the side effects normally accompanying pain management. *Methods*: A literature review was performed on chronic pain, opioid use, and cannabis. Exclusions included articles not in English and published between 2012-2017. *Results*: Recent studies have assessed the usefulness of cannabis and cannabinoids in chronic pain. The challenge of the majority of these studies is the small population subset, the varied types of pain analyzed, and general assessment of pain. Although cannabis can provide a route to avoid the chronic use of prescription opioids and reduce the tolerance and withdrawal from these medications, cannabis itself has side effects to be considered. *Conclusion*: The current opioid epidemic potentially could be remedied by medical cannabis but adverse effects should be adequately identified.

Keywords

Cannabinoids, Chronic Pain, Analgesics, Opioids

1. Introduction

Chronic pain is a disabling, expensive, and prevalent condition. As one of the leading causes of disability worldwide, chronic pain places a significant burden on the healthcare system. Annual costs in the United States alone peak at 500 billion dollars indicating a huge societal impact. [1] Around 126 million adults report pain in the last 3 months and around 25 million report chronic pain in the United States. [1] The most common types are lower back pain, neck pain, osteoarthritis but can include migraine headaches, and cancer related pain. [2]

With such high prevalence of pain, pain management has struggled to resolve this healthcare problem. Pain management has generally been subdivided into two categories: cancer-related pain and non-cancer related pain. The understanding and treatment of pain has been evolving over the past few years and continues to do so. Medications are approached as analgesic, analgesic adjuvant, and multipurpose analgesics. Analgesic adjuvants are defined as medications used to treat other conditions that have been found to be useful in pain particularly in patients receiving opioid treatment. Multipurpose analgesics refer to medications that treat variety types of pain such as glucocorticoids, antidepressants, alpha-2-adrenergic agonists, cannabis, topical therapies, and cannabis. With increased concern over the use of opioid analgesics, alternative treatments are being explored. Many of the alternative treatments have been found to be ineffective. More recently, some trials have explored the use of marijuana in chronic pain. These trials focus on neuropathic chronic pain and marijuana, relying on synthetic cannabinoids primarily. [2, 3]

2. Study Methods

A full literature review of Cochrane, EMBASE, PubMed, UpToDate, and Clinical Key was performed for relevant published articles to marijuana, chronic pain, and consequences of use. Articles were assessed on their thoroughness, relevance, and supportive evidence within the last few years. Articles were also restricted to those in English. All studies were included that were found to be discussing cannabis/marijuana and chronic pain in combination as few articles have been published in this regard. Articles were assessed for bias by analyzing any connections between the authors and the funding sources.

3. Discussion

Cannabinoids specifically are derived from the cannabis plant that contains many compounds, including over 60 cannabinoids with the most potent psychoactive compound being delta-9-tetrahydrocannabinol (also known as THC or dronabinol). THC interacts with the endogenous system that includes endocanniboids and other receptors in the central and peripheral nervous system. There are 2 cannabinoid receptors: CB1 and CB2. CB1 receptors are located in the brain, spinal cord, and on primary sensory nerve terminals. [4] CB2 however is found on microglia, monocytes, macrophages, and lymphocytes. [4] CB1 reduces pain transmission both peripherally and centrally. [4] CB2 receptors are involved in the response for decreased peripheral inflammatory cells mediator release and plasma extravasation. [4] The majority of studies assessing cannabis in pain management have primarily been limited by patient population, which have normally enrolled less than 50 patients. Another limiting factor is the legalities that hinder much medical research and testing. The United States has approved two cannabinoids, dronabinol and nabilone, for use in chemotherapy induced nausea and vomiting and also in appetite stimulation in wasting illness such as anorexia nervosa indicating the safe usage of cannabinoids. Other countries, the United Kingdom, countries in Asia, Africa, and the Middle East, have approved nabiximols, a nasal spray, for treatment of spasticity in multiple sclerosis and as an adjunctive analgesic in adult patients with advanced cancer. Many studies exist that suggest these compounds and smoked cannabis may be useful as multipurpose analgesics in the palliative setting but few studies have focused specifically on cancer patients and chronic pain. [4, 5]

3.1. Efficacy

A study by Lee et al investigated the significance of amygdala activity and the effect of cannabis on pain perception. Amygdalae project to integral parts of the brain, including the dorsomedial thalamus, the thalamic reticular nucleus, the nuclei of the trigeminal nerve, the facial nerve, the ventral tegmental area, the locus coeruleus, and the laterodorsal tegmental nucleus. These connections allow the amygdalae to function in smell, pheromone processing, emotional arousal, emotional learning, memory storage and modulation, fear conditioning, anxiety and stress, aggression, social functioning, binge drinking/alcoholism, and even political orientation. [7] Demonstrated using a functional magnetic resonance imaging (MRI), it was found that there was no significant effect of THC on the perceived pain intensity, which had no changes. However, THC relieved the perceived unpleasantness of pain and hyperalgesia induced by capsaicin, which is well recognised to cause pain in certain doses. THC increased amygdala response during noxious stimulation and indicates the amygdala activity contributes to inter-individual variation in drug tolerances and response. [7]

A study published by Berengere, et al, found that of all alternative treatments for chronic pain, cannabis, guided motor imagery, and Compound Kushen injection were the most promising for pain relief. [8] Some studies have shown that medical cannabis for cancer pain management does have some therapeutic potential but the lack of dosing guidelines and presence of side effects remains a challenge. [9, 10] Inter-patient variability has been found indicating dosage can vary widely from patient to patient. In cancer specifically assessing the side effects can be very difficult and requires a highly trained and astute clinician as complex pathophysiology is in effect. [9] Side effects have been found to be dosage dependent. They normally occur in patients on higher dose and these patients experience little or no side effects upon dose reduction. [9]

A 2013 study focusing predominantly on neuropathic pain found that low dose vaporised cannabis was as effective as the medium dose of traditional neuropathic pain of anti-seizure medication. Little psychoactive effects were reported and if reported were of short duration. [5] A 2015 study of 178 patients demonstrated that inhaled cannabis provides short-term relief from chronic neuropathic pain for 18-20% of patients. [6] The inhalation route leads to a higher peak level quicker than the oral route and higher bioavailability but hasn't yet been observed to have greater evidence in treating neuropathic pain. [11] A questionnaire in a group with spinal cord injuries indicated that 59% of these patients reported a good effect on pain and spasticity with side effects being mood related. [12] A 2017 study of cannabis extract in rats showed that pain from streptozotocin-induced diabetic neuropathy was reduced. [13]

Fitzcharles et al attempted to demonstrate the effects of medical cannabis with rheumatic diseases in mind but was unsuccessful. Cannabinoids were well tolerated in the patient group but ultimately did not show improved pain outcomes when compared to the placebo. [14] The limitations of this study include a small sample size (58 patients) and a duration of 5 weeks.

As of 2016, no published studies demonstrate the efficacy of medical marijuana or pharmaceutical cannabinoids for pain control in children or adolescents. [15] Adult studies did demonstrate at least a 30% reduction in pain particularly in neuropathic pain, cancer pain, diabetic peripheral neuropathy, fibromyalgia, HIV-associated sensory neuropathy, multiple

sclerosis, central pain, non-cancer pain and chemotherapy induced pain with the majority of these studies focused on neuropathic pain. [16] A 2012 study in the UK showed a rate of relief from muscle stiffness (after 12 weeks) that was twice as high with cannabis extract compared to the placebo effect. This was redemonstrated in the same study at 4 weeks, 8 weeks, and for all category-rating scales allowing extract of cannabis to be deemed highly effective in muscle stiffness related to MS. [17]

3.2. Opioids and Cannabis

A statistical association exists between recent cannabis use and lower frequency of nonmedical opioid use among people who inject drugs. Around 50% of people who inject drugs in this study group (San Francisco) were found to have used cannabis in the last 30 days. This suggests that these users use cannabis to reduce their pain or their nonmedical use of opioids allowing a possible adjunct treatment to opioid usage to emerge. [18] Furthermore other studies found that using cannabis resulted in a 64% lower rate of opioid use in patients [19] with overall chronic pain and allowed patients to have an overall better quality of life with reduced medication side effects. [1, 20]

The data does not support recreational cannabis use leading to opioid use. Similarly the difference between episodic use vs. chronic everyday and the associated efficacy in pain has not been studied in depth.

3.3. Dosing

Dosing strategies are one of the major obstacles in medical marijuana. Several studies on HIV and post-traumatic neuropathy have advised 3-4 inhalations daily for five days and this dose was found to be effective. [5, 6, 21] In a study of neuropathic pain the dose was advised to be nine inhalations over a single 6-hour session. [5] For MS related pain and spasticity, it has been found to be effective with a single inhalation of 4% THC cannabis for three days (reference required). The concentration varies even more between many studies with vaporised doses at 1%, 4%, and 7% for diabetic neuropathy and a low dose of 1.29% in one study and the medium dose found to be 3.53%. Comparatively edibles were more likely to have more significant side effects at any dosage level. [22] Overall, patients should start at a very low dose, with several minutes between puffs. [23] For edible cannabis products, patients should wait 30-60 minutes between bites (references required). Typical rolled marijuana cigarettes contain somewhere between 500 and 1000 mg of cannabis plant matter with a THC content between 7.5 and 225 mg with only 25% absorbed systemically (references required). Vaporised marijuana is thought to confer less risk compared to smoked marijuana to cardiovascular and pulmonary function. [23]

3.4. Consequences

Cannabis in general has several very widely known adverse effects: increased appetite, dry mouth, tachycardia, conjunctival infection, which are seen within two hours of use. Additionally, depending on the individual some will demonstrate euphoria while others will be relaxed, sedated, or anxious. Chronic use can lead to more severe adverse effects, affecting the overall psychiatric, neurological, respiratory, endocrine, and gastrointestinal baselines. [24]

Chronically, cannabis use is tentatively associated with persistent neuropsychological deficits even after a period of non-use. [25] Although not concrete data, studies focused on neuropsychological deficits have indicated clinically important adverse effects. [11, 26, 27] Additionally evidence supports restricting the use of cannabis for any reason in several groups: patients younger than 25 years of age, current/past/or strong family history of psychosis, patients with current substance abuse disorder including cannabis, those who are pregnant or becoming pregnant, and patients with current cardiovascular or respiratory disease. [11, 27] Patients younger than 25 years of age using marijuana have been shown to be at increased risk for psychosocial harm, crime, suicidal thoughts, illicit drug use, and long-term cognitive impairment. [26, 15, 28] Side effects demonstrated in Cannabis use disorder (CUD), or the continued use of cannabis despite clinically significant impairment, [29] are found to be the same in medical marijuana smokers as in recreational smokers. Cannabis, as shown in Table 1, is contraindicated in patients with current substance use primarily due to the interaction between cannabis and higher doses of opioids, alcohol, and sedating drugs and that patients are more likely to worsen their current addictions and create a refusal to try non-pharmacological methods for pain management. [11, 14, 27] In regards to cardiovascular and respiratory disease, cannabis use causes physiological changes including elevations in blood pressure and heart rate, catecholamine release, postural hypotension, reversible cerebral vascular syndrome, elevations in carboxyhemoglobin, and impaired respiratory function and chronic obstructive pulmonary disease.

Table 1. *Contraindications to cannabis treatment.*

Contraindications to cannabis treatment
Current, past, or strong family history of psychosis
Pregnant or planning to become pregnant
Younger than 25 years of age
Current/past cannabis use disorder
Current substance use disorder
Respiratory disease
Cardiovascular disease

Discovery of cannabinoid hyperemesis syndrome (CHS) suggests more severe sequelae of chronic cannabinoid use compared to sporadic use. [30, 14] CHS is a syndrome characterised by recurrent cyclical vomiting and associated with abdominal pain and compulsive bathing. This syndrome has been reported in both adults and adolescents but is under diagnosed in the adolescent population. [30] The treatment for this condition is avoiding cannabis use and avoiding repetitive hot showering, as CHS is unresponsive to anti-

emetics. [28, 30] This condition can take a week to fully resolve and is likely to reoccur if cannabis is used again. In the case report reviewed, this seventeen year old reported to emergency care five times over a one year period for uncontrolled nausea, profuse vomiting, and weight loss suggesting this condition can become quite severe and may result in metabolic acid-base imbalances. [30]

Specifically a pair of case studies by Rabner et al, following a traumatic brain injury in adolescents with heavy cannabis use, suggested cannabis use might be a neurological stressor and risk factor for psychosis. [26] The risk for psychosis is thought to be due to similar neuronal signalling pathways involved in cannabis ingestion and TBI recovery as in the CB1 receptors of the endocannabinoid system and the allostatic load model. [26] The most significant effect in adolescents, if only because it is the most studied, is the effect on the brain suggesting marijuana should not be used until the brain has completed development in the mid-20s as these effects can be irreversible. Cannabis causes short-term memory impairment, decreased concentration and attention span, and altered problem solving capabilities. One study of adolescents with ADHD who were regular marijuana users discovered an association between impaired functioning if marijuana was used prior to age 16, but not after this age. [15] Also associated with chronic use is an increase in generalised anxiety and panic attacks, measured at 20-30% increase. [28] Psychologically, cannabis is thought to worsen existing depression and increase the risk of psychosis in those already diagnosed with schizophrenia or those genetically predisposed to schizophrenia. [28] Chronic use in teenagers has also shown to have lower high school completion rates as well as lower college degree acquisition; this is thought to be associated with an unknown effect on the developing brain. Unemployment, criminal activities, and lower satisfaction with life have also been associated with adolescent use. With regards to the respiratory system, use is linked to increased irritation, swelling, and secretions of the airways worsening cough, infection risk, asthma, and chronic bronchitis and even increased development of COPD. [21, 28] Although chronic marijuana smoking hasn't been associated with increased risk of lung cancer, it has not been ruled out. In the endocrine system, cannabis causes an imbalance in hormone production in both women and men resulting in decreased libido, sperm count, and gynecomastia in males and galactorrhea in females. In both sexes, it inhibits growth hormone, secretion, thyroid function, and glucose levels. [28]

Some studies have found short-term adverse effects to include dizziness, dry mouth, nausea, fatigue, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination. [2] Withdrawal symptoms include anxiety, headache, depressed mood, weight loss, anger, aggression, shakiness, abdominal pain, chills, sweating, and hypersomnia. [28] It is estimated around 67% of adolescents who are dependent will experience these withdrawal symptoms which can last up to 14 days. [28]

4. Conclusion

Recent studies (DATES) have assessed the usefulness of cannabis and cannabinoids in chronic pain. The challenge of the majority of these studies is the small population subset, the varied types of pain analyzed, and general assessment of pain. Although cannabis can provide a route to avoid the chronic use of prescription opioids and reduce the tolerance and withdrawal from these medications, cannabis itself has side effects to be considered. An area of major concern is the perceived lack of consequences, especially in the adolescent population, of chronic cannabinoid use. Overall the literature indicates use in children, specifically under the age of 16, should be heavily limited but also chronic use in adults should be avoided until both beneficial and adverse outcomes are known.

Interestingly, a general consensus has been reached in the literature that cannabis use can help those addicted to opioids by reducing the MEDD (morphine equivalent daily dose) and overall life-long risk. Cannabinoids can be used to wean patients off opioid therapies quite effectively although guidelines are lacking. Cannabis possesses fewer side effects compared to opioids and significantly less addictive properties. Guidelines are needed to establish which patients can benefit from this use after assessment of the benefit-risk ratio as risks do exist for certain populations: those with cardiovascular disease, respiratory disease, gastrointestinal disease, pediatric patients, and pregnant women. It is possible that the current opioid epidemic could be remedied by medical cannabis but adverse effects should be adequately identified so this does not result in cannabis use as the next epidemic.

Future studies should recruit more patients, analyse the differences in the pharmacokinetics and pharmacodynamics between patients and substance, dosage levels and, better exploration of side effects.

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