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A STUDY REVIEW OF CANNABIS USE WITH CANCER PATIENTS

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ABSTRACT

Introduction: Cancer patients frequently experience debilitating symptoms such as pain, chemotherapy-induced nausea and vomiting (CINV), and cachexia, significantly impacting their quality of life. Cannabinoids have been suggested as potential therapeutic agents for these conditions. Our review takes a look into medical studies to show potential benefits and side effects of the drug.

Aim of Study: This systematic review is looking for evidence on the efficacy and safety of cannabinoids in managing chronic cancer pain, CINV, and cancer-related appetite and cachexia.

Materials and Methods: A systematic review of PubMed and Google scholar literature was searched using the terms "cannabis" "cancer," and either "pain" or "CCINV" and "cachexia" with studies read for relevance and objectivity.

Results: The evidence regarding cannabinoids for chronic cancer pain is mixed, with some studies suggesting benefits for neuropathic pain, while others show limited efficacy, particularly in opioid-resistant cases. For CINV, certain cannabinoid combinations (e.g., THC:CBD, nabilone) demonstrated effectiveness when standard antiemetics were insufficient, however with potential side effects. The impact of cannabinoids on appetite and cachexia is also inconclusive, with some studies showing potential benefits, but larger trials often failing to demonstrate significant advantages over placebo.

Conclusion: There are many myths and disinformation about cannabis in the public eye. Some glorify it, others condemn it. Studies on CINV and neuropathic pain clearly show that cannabis has antiemetic and analgesic properties. Unfortunately, cannabis does not have an analgesic effect in cancer pain, especially when it comes to pain that is resistant to opioid treatment. When it comes to stimulating appetite and cachexia, the research is very inconclusive, and further studies are needed to evaluate this problem.

KEYWORDS

Cancer, Cachexia, CINV, Cannabis, Pain

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1.Introduction**1.1Medical history of cannabis**

Hemp has been utilized for thousands of years in medicine, construction, and religion. In ancient China, it was a remedy for gout, rheumatism, and menstrual pain. In the Middle East, it served as an antispasmodic and pain reliever, particularly for labor pains. The Arabs employed it as an anesthetic, sedative and also in epilepsy treatment.¹ This rich history of cannabis, particularly its medical applications, finds a fascinating echo in today's scientific research, which is exploring its potential for many of the same, or similar, conditions.

1.2General information about hemp

We can divide cannabis into three subspecies (strains): Cannabis sativa, Cannabis indica, and Cannabis ruderalis². Cannabis sativa plants are typically tall and slender, known for their stimulating, uplifting and energizing effects.³ Cannabis indica plants are shorter and bushier, often associated with relaxing and calming properties.³ These strains contain two primary psychoactive compounds: THC (9-delta-tetrahydrocannabinol) and CBD (cannabidiol). THC is the main psychoactive component, responsible for the euphoric effect, but can also produce anxiety and paranoia. THC has shown its anti-emetic, appetite stimulant, analgesic effects.⁴ CBD is a non-psychoactive compound that does not produce a "high." CBD has demonstrated anti-addictive, anti-anxiety effects and may reduced acute psychotic episodes in patients with schizophrenia.⁵⁻⁷ The ratio of THC to CBD varies among marijuana strains, influencing the overall effects.³

1.3 Endocannabinoid system

The cannabinoid system is a signalling network consisting of endocannabinoid receptors, endogenous cannabinoids and enzymes that influence their synthesis and degradation. It helps cells communicate with each other and maintain homeostasis..

Two primary cannabinoid receptors, CB1^{8,9} and CB2. CB1 receptors, predominantly situated within the central nervous system, play a pivotal role in modulating cognitive functions, emotional responses, and motor control. Endocannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), act as endogenous ligands, binding to these receptors and initiating a cascade of intracellular signaling events. CB2 receptors, primarily located within the immune system, modulate immune cell function and inflammatory responses.

Balance and interaction between individual receptors of the endocannabinoid system affect pain perception,^{11,12} appetite regulation^{13,14} and mood modulation¹⁵. Enzymes responsible for the synthesis and degradation of endocannabinoids ensure precise control over ECS activity, maintaining a delicate balance necessary for optimal health. The ECS's pervasive influence underscores its significance as a therapeutic target for a multitude of clinical conditions, ranging from chronic pain and neurological disorders to inflammatory diseases.

3. State of Knowledge

Use of cannabis among cancer patients

Cancer patients suffer from a range of symptoms, including pain¹², chemotherapy-induced nausea and vomiting (CINV)¹⁶, loss of appetite¹⁷.

3.1 Chronic cancer pain

The analgesic efficacy of cannabis differs according to type of pain. Cannabinoids demonstrate applications in the management of chronic^{11,18}, neuropathic pain¹¹, a pain modality frequently encountered in neoplastic disease. Furthermore, they are being explored for pain management in pediatric populations¹⁹. Oncological pain presents with diverse etiologies, including a neuropathic component often refractory to conventional analgesics. Cannabinoids, through their interaction with the endocannabinoid system, exhibit potential in alleviating this pain.²⁰ The scientific literature presents disparate findings regarding the efficacy of cannabinoids in oncological pain management. Some studies indicate benefits, particularly in neuropathic pain, while others fail to demonstrate significant effects.¹⁹

Cancer patients often deal with pain. It's a very common problem, affecting about half of everyone who has the disease. According to review and meta-analysis by Marieke H.J. van den Beuken-van Everdingen et al.¹² approximately 50.7% of cancer patients experience pain at various stages.

Findings from Johnson et al. (2013) indicate that long-term administration of THC/CBD spray was well tolerated, maintaining consistent effectiveness in the relief of cancer-induced pain. Importantly, patients on ongoing treatment didn't require higher doses of the study medication or extra painkillers. This suggests cannabinoids could be a useful complementary approach to pain relief in cancer care²¹

Nabiximols demonstrate potential analgesic efficacy as an adjunct to opioid therapy in refractory cancer pain. This suggests a valuable alternative to opioid rotation, offering improved pain management. Further studies are warranted to confirm efficacy, optimize dosing, and assess impact on opioid consumption and quality of life.²²

The latest findings imply that oromucosal nabiximols and THC likely do not provide relief for significant cancer pain that resists opioid treatment, based on moderate-certainty evidence.^{23,24} Furthermore, there's limited evidence indicating that nabilone fails to alleviate pain related to chemotherapy or radiotherapy in patients with head and neck cancer and non-small cell lung cancer.²⁵ Similarly, single doses of synthetic THC analogues appear no more effective than a single, small dose of morphine for moderate to severe cancer pain, according to weak evidence. Additionally, there's limited support for the idea that CBD enhances pain reduction when added to standard specialist palliative care for individuals with advanced cancer.²⁶

3.2 Chemotherapy-induced nausea and vomiting

One symptom that cancer patients suffer from is chemotherapy-induced nausea and vomiting, according to research conducted by Doranne L. Hilarius et al. in the initial treatment cycle, a significant portion of patients experience nausea, with 39% reporting acute nausea and a larger 68% reporting delayed nausea.²⁷ Vomiting is less common, affecting 12% acutely and 23% in a delayed manner.²⁸

The physiology of vomiting and dizziness caused by chemotherapy is complex. It involves receptors and transmitters from the central nervous system and the digestive system. Among neurotransmitters such as neurokinin-1, serotonin, and histamine, there are also cannabinoids (CB1)²⁹. Because the receptors for these particles are located outside the blood-brain barrier, after the administration of chemotherapy and their release by damaged cells, vomiting reflexes occur. Beyond these direct effects, higher cortical functions, mediated by the limbic, vestibular, and cerebral cortex systems, can also lead to emesis in response to pain, depression, vertigo, motion sickness, or conditioned responses.⁸

When standard medications for chemotherapy-induced nausea (CINV) and vomiting fail, a mixture of THC:CBD cannabinoids shows promising results.^{30,31} Patients using the mixture, compared to patients given a placebo, stopped vomiting and feeling dizzy, and experienced an overall improvement in quality of life. The THC:CBD group experienced few side effects, such as temporary anxiety, drowsiness, and dizziness.^{30,31} Two patients discontinued the drug due to neuropsychiatric symptoms. No other acute episodes were observed. The THC:CBD dose used in the study was 5 mg. Due to the small number of studies and participants, it is recommended to use a lower dose of THC:CBD at the beginning of treatment, e.g., 2.5 mg.^{30,31}

It's been demonstrated that cannabinoids can impact various medical conditions, notably CINV. Nabilone, a modern synthetic cannabinoid, has been utilized for a considerable period to alleviate vomiting and has shown to be effective in patients battling CINV. This medication could be beneficial for patients who don't achieve adequate control of their nausea and vomiting with 5-HT₃ receptor antagonists and aprepitant. Pre-clinical investigations also suggest nabilone's potential in treating anticipatory nausea. More research into nabilone as a supplementary or emergency therapy is needed in these contexts.³²

3.3 Appetite and cachexia

Cachexia is a wasting syndrome characterized by weight loss, progressive loss of fat and muscle mass, and a decrease in the overall level of protein in the body. Its consequences may include hypoalbuminemia, edema, shortness of breath, chronic fatigue, bleeding, and blood clotting problems. Cachexia can be caused by diseases of the digestive system, such as short bowel syndrome, but also by a lack of food intake, as is the case with cancer. Approximately 50% of cancer patients have problems with appetite and cachexia.³³

To illustrate the mechanism of hunger, the body's energy homeostasis must first be considered. Energy reserves, derived from food, are essential for optimal physiological function. Depletion of these reserves triggers ghrelin release from the gastrointestinal tract, which stimulates the hypothalamus, inducing hunger. This also activates the ventral tegmental area, enhancing dopamine production and pleasure sensations. On the other hands, leptin release during energy satiety inhibits hunger by signaling fullness to the hypothalamus. Furthermore, leptin antagonizes anandamide, which shares receptors with THC.

THC, however, activates hunger. A 2014 study demonstrated THC's significant impact on olfactory bulb activation, sensitizing olfactory and gustatory senses, thereby increasing appetite. A 2015 murine study by Yale School of Medicine further revealed that THC modulates hypothalamic function, promoting ghrelin production over leptin, even post-satiation.

Studies suggest that cannabis may have an impact on metabolic hormone secretion and appetite modulation.³⁴ THC may influence the taste and smell of certain foods and drinks and make them more interesting and enjoyable for cancer patients.³⁵

Studies conducted by T.D. Brisbois et al. showed that for the THC group, SLIM appetite scores increased relative to baseline and placebo. The majority of THC-treated patients (64%) had increased appetite, three patients (27%) showed no change and one patient's data were incomplete. No THC-treated patients showed a decrease in appetite. By contrast, the majority of patients receiving placebo had either decreased appetite (50%) or showed no change (20%).³⁵

Studies conducted by F. Strasser et al. showed no differences between the three groups (patients taking cannabis extract, THC and placebo) over 6 weeks of treatment for the primary end points of appetite, for cannabinoid-related toxicity, or for secondary end points such as mood or nausea.³⁶ Like the recent North Central Cancer Treatment Group phase III trial using the same dose of THC, in which 49% of patients receiving THC had better appetite at least once during the study, our study showed every two weeks appetite scores

higher than baseline values at some point during the trial in more than 50% of patients in all three groups.³⁷ Like previous trials for symptom control, our study showed significant placebo effects. No differences in toxicity ascribed to cannabinoids were found between treatment arms in either this or the North Central Cancer Treatment Group phase III trial.³⁶

Conclusions:

This systematic review of scientific research and medical literature summarizes the therapeutic effects of cannabinoids and their side effects in cancer patients.

Cannabinoids have little effect on cancer pain in oncology patients. Oral and mucosal nabiximols do not have analgesic effects on pain associated with chemotherapy and radiotherapy, especially opioid-resistant pain.^{22,23} something something something some some someeee someee. Patients can only expect pain reduction in the case of neuropathic pain, as shown by studies.¹¹

Scientific studies show very promising results for chemotherapy-induced nausea and vomiting (CINV). THC:CBD therapy in the same concentrations has an antiemetic effect, while other methods and pharmacological agents are ineffective and do not work.^{30,31,38} Nabilone also has antiemetic and anti-nausea effects, whereas other agents are ineffective.³² However, when using both natural and synthetic cannabinoids, side effects such as anxiety and dizziness have been reported.^{30,31,38}

In the area of appetite and cachexia, the mechanisms of action of THC in stimulating appetite are promising, through its influence on hormonal pathways and the central nervous system. However, the outcomes of clinical trials evaluating the efficacy of cannabinoids (including standardized cannabis extract and pure THC) in improving appetite and quality of life in patients with advanced cancer and cachexia are inconsistent.³⁹ While some studies indicate appetite improvement in a subset of patients, others, including a phase III trial, did not demonstrate significant differences compared to placebo.³⁶ Notably, a significant placebo effect was observed regarding appetite.

It is very important to conduct more clinical trials, randomized trials on larger groups of people. Specific patient groups, such as cancer patients, should be taken into account. The dosage and route of administration of cannabis should be precisely determined: oral, inhalation. This is certainly a major challenge in the case of vaporization. Attention should also be paid to the interaction of cannabis with other drugs, such as opioids, and to potential side effects. It is worth remaining skeptical and objective when it comes to cannabis, as its marketing and advertised health benefits are greatly exaggerated.

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