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REVIEW: THERAPEUTIC EFFECTS OF CANNABIS IN TREATING CANCER-RELATED PAIN.

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Abstract

Pain is a prevalent symptom of cancer and a side effect of cancer treatments. Opioids and non-opioids are the commonly used analgesics in treating cancer related pain. Historical evidence and scientific data suggest that cannabinoids from the cannabis herb have analgesic properties. Recent studies conducted at Pain Relief Unit, Hadassah-Hebrew University Medical Center in 2016, Seattle Cancer Care Alliance in 2017, and Tikun-Olam Ltd in 2018 were reviewed to confirm whether cannabis have any therapeutic effects and if so what is the efficacy and safety of medicinal cannabis use on pain relief and quality of life. Background of cannabis, the mechanism of action of cannabinoids, legal aspects, adverse effects and other analgesics were also reviewed in this article.

Key words- *Cancer, cannabis, cannabinoids, cancer pain*

Abbreviations

THC- Tetrahydrocannabinol
CBD- Cannabidiol
S-TOPS- Short form- Treatment Outcomes in Pain Survey
DMARD- Disease-modifying antirheumatic drugs
SNRI- Serotonin–norepinephrine reuptake inhibitors
SSRI- Selective serotonin reuptake inhibitors

1. INTRODUCTION

Cannabis Sativa, also known as cannabis or marijuana, is a plant of the plant family Cannabaceae [5]. Although the use of cannabis is highly stigmatized, evidence for the uses of the psychotropic effects of cannabis for medicinal use has a history of about 4000 years [4]. Compounds present in cannabis are known as cannabinoids, as they act as cannabinoid receptor agonists. The most common cannabinoids used for medical purposes are THC and CBD [11].

Cancer is an emerging global pandemic with growing incidence and mortality. According to the International Agency for Research on Cancer, 9.6 million deaths recorded in 2018 were cancer-related [10]. Changes in the body due to cancer can manifest through various symptoms. The effective treatment of cancer involves an aggressive regimen of treatments that can have debilitating effects on patients. Cancer condition and the corresponding treatments, such as chemotherapy, can have side effects such as nausea, vomiting, anorexia, malabsorption, weight loss, anemia, fatigue and pain on the body. These are major contributors to the decrease in the quality of life of such patients [20]. The scope of this article will be limited to pain associated with cancer.

Cancer pain can be caused by inflammatory, ischemic, neuropathic, and compressive mechanisms caused by the invasion of cells at multiple sites of the body and also due to the aggressive treatments utilized to combat the life-threatening disease [23]. Healthcare providers, in their exploration of new avenues of treatments to increase cancer patients' quality of life by reducing pain, have turned their attention to the therapeutic potential of cannabis with the growing body of scientific evidence. The therapeutic value of cannabis-based treatments must be weighed against the potential risks and local legislative constraints.

2. METHODOLOGY

A search of literature published in Google Scholar was conducted using search phrases such as "cancer pain", "therapeutic uses of cannabis", "cannabis for cancer", and "medical cannabis". All literature before the year 2010 was excluded to reduce the likelihood of using outdated information. Articles addressing chronic non-cancer pain were also excluded. Research studies and literature between 2010 and 2019 were used for the reviewing of cancer-related pain management using cannabis derivatives and the comparison of non-cannabinoid analgesic treatments with cannabinoid treatments.

3. MAIN CONSTITUENTS OF CANNABIS

21 carbon terpenophenolic compounds produced by Cannabis sativa plant, that can act on specific receptors in the brain and body, are defined as cannabinoids [2,9]. Main active ingredients of cannabis include delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [17]. Cannabinoids from the cannabis plant are classified as phytocannabinoids.

The primary psychoactive component of cannabis, THC, produces its effects in the body by the activation of G-protein coupled CB1 and CB2 receptors [13]. They can be identified as receptor agonists. Humans also produce cannabinoids inside the body. These cannabinoids are part of the endocannabinoid system, which is responsible for the changes in intracellular signaling when bound to CB1 and CB2 receptors [1]. The activation of these receptors trigger reactions resulting in reducing pain, stimulating appetite, increasing digestion, and changing emotions and thought processes [17]. CB1 receptors are located primarily in central and peripheral neurons [15]. Majority of CB2 receptors are found on immune cells such as B lymphocytes and natural killer cells.

CBD is a compound with low affinity for CB1 and CB2 receptors. CBD is seen having antagonistic effects on CB1 and CB2 receptors when present in relatively low concentrations. These antagonistic effects are responsible for its anxiolytic, anticonvulsive and antipsychotic properties. CBD may also be playing a role in countering psychoactive effects of THC to some degree [15].

4. CANNABIS PREPARATIONS AND CURRENT MEDICAL USE

Increase in demand as well as legalization of cannabis in some parts of the world have expanded the way cannabis is available. Herbal form of cannabis is available as hashish and marijuana that can be smoked through rolled cigarettes. Cannabinoids that are extracted from the plants are used to make drugs such as dronabinol and nabiximole. There are also structurally similar compounds known as analogues that are synthesized to mimic the cannabinoid to the endocannabinoid system. Some of these synthetic drugs are levonantradol and nabilone [22]. An oromucosal spray containing THC, called Sativex, is being tested to be used as a safer alternative to cannabis cigarettes [14]. It is also more effective in its absorption in comparison to other cannabinoid oral drugs which has low bioavailability due to the acid in the stomach.

5. CANCER PAIN RELATED RECENT RESEARCH STUDIES

6. 5.1 A study on the effect of medicinal cannabis on pain and quality of life (1)

In 2016, a study was done to determine the effect of long term medicinal cannabis treatment on pain in patients with treatment-resistant chronic pain. Criteria for test subjects to be included in the study were age older than 18 years, presence of chronic pain lasting 3 months or longer, and possessing unsatisfactory analgesic response or side effects with at least two analgesics from two different drug classes at full dosage. Each of the participants was required to intake 20 grams of cannabis, containing 6-19% THC and 0.3-5.5% CBD, per month through cigarettes, baked cookies or oil extracts. Participants were instructed to record each cannabis dose starting with one cigarette puff equivalent to 1 drop of the cannabis oil per day, and increase by 1 puff /drop per dose, to a frequency of up to 3 times a day until pain was alleviated or side effects appeared [12].

176 participants completed the study after a mean follow-up of 7 months. According to the S-TOPS (Treatment Outcomes in Pain Survey – Short Form) questionnaire data from the study, pain symptom score improved from 83.3 to 75.0 in 65.9% of the participants. 6.8% of the participants were suffering from cancer pain [12].

7. 5.2 A study on cannabis use among patients at a cancer center (2)

A cross-sectional anonymous survey of cancer patients was conducted between 2015 and 2016 at the Seattle Cancer Care Alliance, which is a National Cancer Institute assigned cancer center, over 6 weeks. Inclusion criteria for the study included age of 18 years or above, English speaking, and not having completed the questionnaire at a prior appointment. Each participant was given the survey assessing the information regarding cannabis use and their clinical risks and benefits. Urine samples of less that 1ml were obtained and stored anonymously to screen for cannabinoids [21].

926 participants completed the study. According to the data gathered in this study, 24% of the participants considered themselves active cannabis users. Among these active users, data showed that the most frequent use of cannabis was for pain relief [21].

8. 5.3 A study on the safety and efficacy of medical cannabis in a population of cancer patients (3)

A research done at Tikun-Olam Ltd from 2015 to 2017 aimed to study the epidemiology of medical cannabis treatment-receiving cancer patients. The study also addressed the safety and efficacy of cannabinoid therapy. The study included an extensive initial evaluation of the patient and their medical history, educating the patients on the necessary information about cannabis, and prescribing a cannabis strain based on the THC to CBD ratio appropriate for each patient. A customized approach is taken to ensure each patient is given the suitable method and mode of administration. Titration protocols are also clearly explained to each patient. Safety was studied through follow-ups, recording any adverse conditions that have emerged at 1 and at 6 months after initiating treatment. The efficacy was measured by assessing the pain levels that were being experienced by the patient and the change in quality of life during and after the treatment. Pain levels were measured by using an 11 point scale ranging from 0 being no pain to 10 being worst pain imaginable. Quality of life was measured on Likert scales ranging from very poor, poor, neither poor nor good, good to very good [25]. 2923 patients responded to the intake questionnaire but the response declined to 2082 in the 1 month follow-up and then to 1248 in the six month follow-up. The cannabis treatment was well-tolerated, effective and showed no significant harm to the cancer patients. According to the study, approximately 70% of patients reported an increase in the quality of life after 6 months of treatment. When looking at the pain related data of this study, the most common use of cannabis was for cancer associated pain relief. There is also a significant decrease in high intensity pain in over 50% of the population after 6 months of treatment. Only less that 5% of patients reported to have no decrease in pain after 6 months of treatment [25].

9. ADVERSE EFFECTS OF CANNABIS USE

When tackling this issue of adverse effects, a clear distinction must be drawn between the use of cannabis for therapeutic purposes and recreational purposes. Therapeutic benefits of cannabis can be harnessed even without experiencing its intoxicating effects [8]. Adverse effects were strongly related to the dosage of the drug. Studies show that dosages above 15-20mg of cannabis can result in psychoactive side effects such as somnolence, dizziness, confusion, nausea, and hypotension [6]. Some studies have also linked heavy use of cannabis to reduction in memory, reaction time, attention, and motor function [15]. Impaired motor function accounts for many cannabis related motor accidents. Cannabis possesses the ability to induce paranoia and disorientation in newer users [8].

The method by which cannabis is administered plays a crucial role in the safety of the patient. There are potential health risks that may arise due to the smoking aspect of cannabis. Airway diseases such as bronchitis and oropharyngeal cancers are some of the major possible health risks involved in transitioning to cannabis-based therapies [18]. Due to the lack of more controlled studies and low-strength evidence, no conclusive health risks on the pulmonary and cardiovascular system can be established [19].

10. LEGAL ASPECTS

In the United States, cannabis is classified as a Schedule I agent with a high potential for abuse and has no accepted medical use. All clinical trials conducted on the use of cannabis require a license from the National Institute on Drug Abuse [1]. Due to the growing body of evidence, by 2014, 23 states have passed laws and started medical cannabis programs [3].

United States, Canada, Israel, Netherlands, Switzerland, Czechia, Australia and Germany have allowed cannabis to be used for medical use under conditions specified by the legislation [9].

Cannabis is grown in some parts of Sri Lanka. In the local context, cannabis still remains an illegal drug. Although it is classified as illegal, the use of cannabis has not been lowered, as the majority of drug arrests in Sri Lanka are cannabis-related. The only known medicinal use of cannabis in Sri Lanka is in ayuruvedic treatments but the processing and preparation of the plant is different. Almost all the cannabis confiscated by law enforcement is in the form of unprocessed herb [24].

11. COMMON TREATMENTS FOR CANCER RELATED PAIN

Mild to moderate cancer pain is treated with non-opioid analgesics such as acetaminophen, aspirin and ibuprofen, but moderate to severe pain cannot be alleviated by these drugs. Opioid drugs alone or in conjunction with non-opioid drugs are prescribed to patients with severe pain. Commonly used opioids are morphine, oxycodone, hydrocodone, hydromorphone, codeine, fentanyl, and methadone [16].

Opioid and non-opioids drugs have shown to have a synergistic effect with cannabinoids. Cannabinoids and opioids interact in signal transduction mechanisms in the body [2]. This relationship is shown by the reduction in opioid use when cannabinoid treatments were initiated [7].

Medication type	Use before initiation of cannabis (n/N)	Use after initiation of cannabis (n/N)
Opioids	119/184 (65%)	33/184 (18%)
NSAIDs	115/184 (62%)	38/184 (21%)
DMARD	15/184 (8%)	3/184 (2%)
Anti-depressants	72/184 (39%)	25/184 (14%)
SNRIs	13/184 (7%)	3/184 (2%)
SSRIs	34/184 (18%)	8/184 (4%)
Others	69/184 (38%)	40/184 (22%)

Table 1: Medication Classes Used Before and After Initiation of Cannabis among Study Population [7].

The use of opioids has increased with time and, as a result, opioid-related overdose mortalities have also increased. A research published in 2014 showed that in the United States, compared with states without cannabis laws, lower mean opioid analgesic overdose mortality rates were seen in states with cannabis laws [3].

12. DISCUSSION

Medicinal use of cannabis is highlighted though a number of studies done in murine models as well as human trials. In the study (1), the effect of cannabis on chronic pain was studied. The study (2) showed the analgesic effects that were felt by active cannabis users who were also having cancer. In the study (3), a more comprehensive knowledge was obtained on the efficacy and the safety of cannabis use specifically in cancer patients. There is evidence that there are therapeutic effects of cannabis on cancer-related pain relief but limitations are present in these 3 studies consistent with previously done studies.

Limitations associated with these studies include the lack of a control group, lack of frequent assessment, and not properly analyzing the effect of other opioid or non-opioid analgesics during the time period of the study cannabis treatment [12]. Low response rates due to stigma associated with cannabis and not fitting the inclusion criteria may also be other sources of limitations for these studies [21]. The experiments were conducted in cancer centers. Therefore, the data may be unreliable, as many of the patients were already in the recovering stages or under other medications that may have contributed to the increase in quality of life. Due to availability of many routes of cannabis administration, and the unavailability of highly quantified dosages to the general public, development of proper controlled experimental procedures is difficult. This is further hindered by the availability of many synthetic cannabinoids, which the study population may mistake when doing the research and report as them being active cannabis users.

Another source of error may be due to the subjective nature of pain. In the studies, the quality of life was measured by an ordinal scale where the patient selects the option best describing his/her perception of pain. No two people experience pain the same way. Therefore, no threshold values can be measured to ensure a standardized scale for pain.

Therapeutic effects of cannabis have been observed through many studies. The lack of standardized controlled trials, social stigma and the lack of a large pool of participants are barriers to adapting cannabis as a treatment for cancer pain. Products such as sativex are promising for the future, yet the implementation of medical uses for natural cannabis still needs more testing. Commonly used opioid and non-opioid analgesics have been established through a substantial amount of research and testing. Same level of research and testing must be done to conclusively determine the possibility of cannabis being a readily available treatment for cancer-related pains, either by itself or as an adjuvant. Until such data is available, legal restrictions are warranted to ensure the safety of the general public from the adverse effects of cannabis on individuals and their surroundings.

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