



## Cannabis as an Alternative Treatment for 11 Medical Conditions: a Literature Review

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**ABSTRACT:** Over the past years, the use of medical cannabis is becoming of interest in the medical world. It has been recognized as an alternative treatment and has been legalized in many countries for medical purposes. Although there have been numerous claims of what cannabis can do, conclusive findings regarding its properties remain elusive. While access to cannabis is high, information accessible to consumers is still limited. Countless past studies have been done on cannabis' effect on health issues. Hence, the purpose of this literature review was to conclude and summarize the past findings on the therapeutic effect of cannabis, focusing on the Delta-9-Tetrahydrocannabinol ( $\Delta^9$ -THC) and Cannabidiol (CBD), on the following medical conditions; chronic pain, opioid use disorder (OUD), obesity, sleep disorders, cancer, post-traumatic stress disorder (PTSD), psychosis, epilepsy, traumatic brain injury (TBI), Parkinson's disease (PD), and Alzheimer's disease. The risks of cannabis consumption for these issues were also identified. The results suggested that cannabis has the ability to assist in chronic pain, OUD, sleeping disorders, and Alzheimer's disease. Regarding PTSD, psychosis, and TBI, there have been findings only about CBD which showed a beneficial effect on the diseases. It could not be concluded that cannabis can be used to treat obesity, cancer, epilepsy, and Parkinson's disease due to limited evidence. The majority of the studies also demonstrated that high doses of CBD and low doses of THC should be used to maximize benefits. More clinical trials and research need to be conducted as there are research gaps and insufficient information in various subjects.

**KEYWORDS:** Cannabidiol, Cannabis, Delta-9-Tetrahydrocannabinol, Medical Conditions, Therapeutic Effect

### INTRODUCTION

Cannabis plant extracts are becoming of interest to scientists around the world to develop a way to use it for medical treatment, especially among patients who do not respond to conventional medications. Many countries around the world have already legalized and approved cannabis for medical purposes, increasing the availability and accessibility to cannabis. As a medicinal agent, the various biological effects of cannabinoids have been acknowledged as beneficial for a number of diseases [1]. However, basic information about cannabis consumption, such as route of administration, doses, and product formulations, is still lacking. There are numerous forms of cannabis products and wide varieties of administration routes, including inhalation, oral ingestion, topical application, and sublingual administration. Patients can have a hard time making a decision on choosing the forms of product, dosage, and route of administration that are appropriate for their purpose. Furthermore, there are rising concerns regarding how effective the product really is, the potential risks, and their side effects. These concerns will be attended to. The world market on these products is growing rapidly, especially on CBD products. The scientific community has made significant contributions to the development of the cannabis industry. This is evidenced by the increasing acceptance of the drug and its derivatives globally [1]. In 2020, it was estimated that the cannabis market size was valued at USD 20.5 billion globally. The market growth was projected to rise to USD 90.4 billion by 2026 [1]. With the expansion of the cannabis industry expected to increase continuously, more competition in business is definite. Lots of commercial claims regarding the therapeutic effect of cannabis have been made for marketing and profits. However, it is unclear if those claims are backed by empirical evidence.

The use of cannabis as an alternative treatment is still controversial. There are so many studies about cannabis, which could be difficult for patients to comprehend. It is crucial for patients to have the correct information before using cannabis and their concerns must be attended to. This review article determined what is known based on current evidence and what needs more research to be proven. Some of the most debatable issues are chronic pain, opioid use disorder (OUD), obesity, sleep disorders, cancer, post-



traumatic stress disorder (PTSD), psychosis, epilepsy, traumatic brain injury (TBI), Parkinson's disease (PD), and Alzheimer's disease. This review, therefore, aimed to summarize previous findings related to these health issues.

## BACKGROUND

Cannabis refers to a group of plants which contain psychotic properties. It is a genus of annual flowering plants which belongs to the family Cannabaceae [2]. This flowering plant has been used for various purposes for over 5000 years [3]. Primarily, cannabis was used as a source of a stem fiber and a resinous intoxicant [4]. Cannabis is normally categorized as monospecific (*Cannabis sativa* L.) which branches into a few subspecies (*C. sativa subsp. sativa*, *C. sativa ssp. indica*, *C. sativa subsp. ruderalis*, *C. sativa subsp. spontanea*, *C. sativa subsp. kafiristanca*) [5]. An enormous variety of chemicals is present within the cannabis plant. Of the 483 compounds, many identified are distinctive to cannabis, such as, the more than 60 cannabinoids and about 140 members of terpenes [6]. The most studied cannabinoids are Delta-9-Tetrahydrocannabinol ( $\Delta^9$ -THC) and Cannabidiol (CBD), thus, we mainly focused on these two constituents.

CBD and THC share the same chemical formula, consisting of 21 carbon atoms, 30 hydrogen atoms, and 2 oxygen atoms. However, the atoms are arranged differently, resulting in the contrasting chemical properties and its effects on human's body. THC is the most prevalent of the active ingredients of cannabis and is responsible for the main psychoactive effect, or known as the feeling of "high". THC affects the stimulation of dopamine release in the brain, which causes feelings of euphoria. The effect also varies depending on the body's chemistry [7]. The structure of THC is similar to that of the brain chemical anandamide. This makes it possible for the body to recognize its psychoactive effects and alter the normal brain communication. It affects processes related to pleasure, memory, attention, movement, coordination, sensory, time perception, and concentration [8]. CBD, the second most abundant cannabinoid, is the chemical compound touted for a wide variety of health issues. Cannabidiol is not psychoactive and has antineoplastic, anti-inflammatory, chemopreventive and analgesic properties [9]. Human studies did not find evidence of abuse or dependence related to the consumption of pure cannabidiol [10].

Our biological system contains the endocannabinoid system (ECS), which comprises neurotransmitters that bind to Cannabinoid receptors. The ECS can regulate various physiological processes, such as pregnancy and parenting, and is involved in the development of mood and memory [10]. The two primary cannabinoid receptors (CB) are CB1, fundamentally found in the central nervous system with some portion in the peripheral tissues, and CB2 receptors, located in the periphery on cells with immune function, as well as at low densities in the central nervous system [10]. The CB1 receptors are mostly found at highest densities in the hippocampus, cerebellum and striatum. The CB2 receptors are primarily located in the spleen and hematopoietic cells and share just 44% of its nucleotide sequence with the CB1 receptor. [11].

The endocannabinoid system is affected by the use of Cannabinoids and can have an impact throughout the human body physiologically, emotionally, and cognitively. It is known that cannabinoids, mostly THC and CBD, can bind to the CB1 and CB2 receptors and activate various cellular and molecular targets of the endocannabinoid system [9]. THC acts as a partial agonist and binds to CB1 receptors, resulting in the increasing release of dopamine, glutamate and acetylcholine in certain brain regions [12]. Different people experience different pharmacological effects, influenced by the interactions of cannabinoid receptors [10]. Properties of CB receptor agonists are known to include analgesia, muscle relaxation, immunosuppression, anti-inflammation, antiallergic effects, improvement of mood, stimulation of appetite, antiemesis, bronchodilation, neuroprotection and antineoplastic effects [13].

## METHOD

This review article concentrated on the association between cannabis and each medical condition. A thorough examination of the evidence was performed, employing standard methods in literature searches, evidence reviews, grading, and synthesis. Determinations regarding the beneficial effect on each medical condition were then summarized based on the strength of evidence. Articles were searched through Google Scholar using the keywords concerning cannabis association with each medical condition such as "Cannabis and chronic pain", "Cannabis and sleep disorder", "Cannabis and cancer", "Cannabis and epilepsy", and etc. The search drew on relevant articles utilizing a reproducible search method. The search ranged from 2000 to 2021. The following are the inclusion criteria for the articles in this literature review.



- A. Empirical (qualitative or quantitative) data of the relationship between cannabis and each medical condition.
- B. Written in English language
- C. Published in 2000 and later
- D. Conducted in various countries
- E. Dissertations and theses are excluded

## RESULTS

### A. Chronic Pain

#### *General Information:*

Chronic pain is a type of pain that usually persists for longer than several months even after a patient receives medical treatment. People who suffered from severe chronic pain have been reported to have worse health conditions, be exposed to more health care, and have more infirmity than those who had experienced less pain [14]. The pain can either be sharp or dull, causing inflammation at the affected area. Furthermore, the pain can also lead to some major problems, such as sleeping difficulties, anxiety, and depression.

There are many types of chronic pain, including headache, low back pain, cancer pain, arthritis pain, neurogenic pain, psychogenic pain, and postsurgical pain. The cause of chronic pain varies. It can result from surgery or repeated muscle injury, such as back sprain, broken bone or torn muscle. Chronic pain tends to develop when a damaged nerve happens to be in some particular area. Being damaged, the nerve is likely to create more intense and long-lasting pain than normal. However, in some cases the pain does not emerge from any prior reasons, but rather from an underlying disease, for instance, fibromyalgia, chronic fatigue syndrome, endometriosis, inflammatory bowel disease, and so on [15]. Moreover, there is a condition called "Central sensitization" which also involves the development and maintenance of chronic pain. By maintaining the nervous system in a persistent state of high reactivity, this condition heightens the sensitivity to pain of patients as well as their sensation of touch; it can turn a mildest bump into the most painful one for the patients [16].

#### *Current Treatments:*

Because of its complexity and unicity, chronic pain is a very challenging condition to be treated in patients. In order to alleviate the pain, health care providers will try to indicate the cause of the pain first. Then, they may recommend a variety of medications based on the root of the pain. The following treatments are the example of medications used to treat patients with chronic pain.

**Nonsteroidal anti-inflammatory drugs (NSAIDs):** NSAIDs are widely known to be very effective in alleviating mild to moderate pain or conditions associated with swelling and inflammation. Many NSAIDs, such as ibuprofen, naproxen, are not difficult to find and can be bought over the counter. The way NSAIDs work is by blocking an enzyme called "cyclooxygenase (COX)" which is released when the tissue is being damaged. By inhibiting this enzyme, the pain response is temporarily shut down; thus, the pain that an individual perceives is lessened [17]. The strength of NSAIDs varies depending on the dosage and the type of medication. If patients take more than the recommended doses, they may experience side effects, for example, nausea, stomach pain, ulcers. Studies have shown that there are unpleasant effects, adverse gastrointestinal and cardiovascular events, resulting from NSAIDs overdose. On top of that, the risks from NSAIDs overdose also increase with age and in the presence of other health conditions, including diabetes, a history of stomach ulcers, and kidney disease. There is a bottom line on this medication as well. Due to the ceiling effect in this medication, one can only take NSAIDs for a certain period of time. In other words, exceeding the recommended dosage will not only provide no additional benefits, but also increase the risk of experiencing the side effects [18].

**Acetaminophen:** as of today, acetaminophen is the most prevalently used painkiller or analgesic worldwide. It is reported to be effective for mild to moderate pain suffered from osteoarthritis and back pain [17]. According to the World Health Organization (WHO), they recommended acetaminophen to be used as first-line treatment in all pain conditions. However, there are some conflicts of opinion related to this topic whether it is really potent in treating patients with chronic pain or not. Studies have claimed that there is little to no efficacy with skeptical clinical relevance. Further, only a few literatures cited the long-term use of acetaminophen in



chronic pain patients. The mechanism of action of acetaminophen on our body has not yet been fully elucidated; therefore, a lot of studies need to be conducted in order to acquire the utmost potential from it [19].

Opioids: opioid medications or narcotics are synthetic cousins of opium and the drugs derived from opium, such as heroin and morphine. It reduces the pain by interacting with opioid receptors on the nerve cells and, then, sending signals to our body and brain. Their use in the management of acute pain and chronic pain was considered to be the standard of care not long ago, but evidence has suggested negligible differences between opioids and non-opioid medications in terms of improvement in pain, function, mental health status, sleep, or depression [20]. On the other hand, long-term use of opioids can increase risk of serious harms such as physical tolerance, misuse, addiction and unintentional overdose which can lead to death. Currently, because of those harmful risks, opioids are considered to be the last resort of the management of chronic pain [17].

### *Therapeutic Properties of Cannabis on Chronic Pain:*

According to Whiting et al. (2015), there were 28 randomized controlled trials in patients with chronic pain involving 2454 participants that compared cannabinoids to usual care, a placebo, or no treatment. Twenty-two of these trials assessed the use of plant-derived cannabinoid (i.e., nabiximols, THC oromucosal spray and oral THC), five trials assessed the use of synthetic THC (nabilone) and the remaining trial assessed the use of an active comparator (amitriptyline). Most of the studied medical conditions were neuropathic pain and the others were cancer pain, multiple sclerosis, rheumatoid arthritis, musculoskeletal issues, and chemotherapy-induced pain. The result from the plant-derived cannabinoid had shown great improvement of pain by around 40 percent compared to the control conditions. However, all of the cannabis in flower form was provided by the National Institute on Drug Abuse whose quality was different from many of the available cannabis products in the regulated market [21]. Besides, the paper did not provide much information related to the dose, route of administration or side effects of commonly used cannabis products. To ensure the safety of patients, more research is needed to be carried out for the better understanding of any potential benefits and adverse effects related to the possible use of medical cannabis, cannabis-based medicines and synthetic cannabinoids for pain alleviation [22].

The effect of CBD varies depending on the medical condition or disease that one suffers from. CBD tends to be notably effective in managing the pain in some conditions, for instance, multiple sclerosis, spinal cord injury, peripheral neuropathy, kidney transplantation. On the other hand, the outcomes were different in patients with Crohn's disease; the condition did not seem to ameliorate [23]. Study conducted in New Zealand regarding the safety of CBD treatment in patients with non-cancer pain and mental-health symptoms has reported that CBD use showed no sign of any major adverse effects. In fact, the sleep condition and appetite of patients were improved regardless of the difference in doses [24]. THC, on the other hand, when being used in the appropriate proportion, could be effective in relieving neuropathic pain. Cannabis products that contain high concentrations of THC could increase the risks of having cardiovascular disease, acute pancreatitis, cannabinoid hyperemesis syndrome, and occupational injuries. Patients, especially expectant mothers, need to be cautious when using cannabis-related products since this can increase the chance of neonatal morbidity or death. The majority of the studies associated with the treatment of severe chronic pain, which were operated by using Nabiximol, utilized the combination of CBD and THC at 1:1 ratio. This combination lessened the detrimental effects from solely administration of THC. Besides, it has been proven to be effective in reducing the perceived pain in patients with chronic pain, advanced cancer patients and people who suffered post-surgical pain. Although the result was very promising, further research studies on other diseases and medical conditions were still recommended [23].

## **B. Opioids Use Disorder (OUD)**

### *General Information:*

Substances like opioids, heroin, cocaine that induce the circuit, correlated with processing rewards, in the brain will slowly produce a high level of positive reinforcement. Eventually, patients will become physically dependent on this drug and will continue taking them, in spite of the unpleasant side effects. Consequently, patients who cease taking the drug will experience withdrawal symptoms, for example, increasing heart rate, sweating and intense craving for the drug. Additionally, if patients consistently take opioids medication for a certain period of time, they will develop a phenomenon called tolerance. People who developed tolerance will need to consume higher doses of opioids than usual in order to experience the same effects [25]. To be diagnosed with opioid use disorder,



an individual needs to spend a considerable amount of time searching, getting, and taking opioids. He would, also, have to experience significant impairment or distress resulting from the opioid use within a 12-month period [26].

As mentioned earlier, opioids can be used as pain relievers due to their properties to interact with opioid receptors. But due to the fact that it can, also, produce euphoria during the process of relieving the pain, opioids can be misused. In some reported cases, patients develop opioids even when they take prescribed opioids in the proportion recommended by the doctor. Substance use disorders are, actually, brain disorders [25]. There are many factors that contribute to OUD, including, biological, environmental, genetic, and psychosocial factors [27]. Hence, when being exposed to opioids, some individuals are more susceptible to OUD than others [25].

### ***Current Treatments:***

Medication-assisted treatment (MAT): MAT is the use of medications along with counseling and behavioral therapies to treat patients with substance use disorders. This program is designed to be tailored with each individual by means of different approaches. MAT is mainly utilized to treat patients with addiction to opioids. The prescribed medications used in the MAT program, for example, are buprenorphine, methadone, and naltrexone. These medications have properties to manipulate brain chemicals, inhibit the euphoric effect from opioid use and alleviate withdrawal symptoms. Also, they must be able to normalize the body functions without adverse effects and, most importantly, euphoric effects from the medications; since, it can contribute to other substance use disorders. Besides, buprenorphine, methadone, and naltrexone are guaranteed to be safe by the FDA to treat opioid addiction. Other than medications, MAT also provides counseling and behavioral therapies which will help them cope with their behaviors, thoughts, emotions, and the understanding of their current situation [26, 28].

### ***Therapeutic Properties of Cannabis on OUD:***

According to L Hurd et al. (2019), the randomized controlled trial, involving 42 participants, evaluated different types of effects of CBD (400 or 800 mg) or a placebo use on drug craving and anxiety in drug-abstinent patients with heroin use disorder. The researchers classified the effects into three types, including acute effect (within 1 hour, 2 hours, and 24 hours after the administration), short-term effect (once daily administration for three consecutive days), and protracted effect (within a week after the last of once daily administration for three consecutive days). In this study, the researchers used EPIDIOLEX, plant derived CBD in liquid formation. The result was very satisfying. Acute and protracted CBD administration notably lessened both craving and anxiety compared to placebo administration. The drug cue-induced measures of CBD administration, heart rate and salivary cortisol levels, also decreased. Furthermore, there was no sign of effects on cognition or adverse effects [29].

However, another study, H. Epstein et al (2015), assessed cannabinoid use in 116 patients who underwent methadone tapering. All of the participants were either heroin, cannabis or both users. Among them, 46 were also cannabis users. The outcomes showed that opioid-withdrawal scores between cannabis and non-cannabis users did not differ. Nevertheless, some participants who used cannabis had reported increased severity of their withdrawal symptoms [30].

CBD may play an important role in treating patients with opioid use disorder. CBD has been reported to lessen rewarding effects from many drugs of abuse, for example, cocaine, amphetamine, and nicotine. Moreover, there was no sign of adverse effects or rewarding effects in CBD administered individuals. Not only could CBD ameliorate OUD patients' condition, it could also be used to prevent OUD in the first place. Due to the pain relief ability that CBD has, it could be substituted as a pain reliever to opioids. In contrast, it was plausible for higher concentrations of THC, unlike CBD, which was a rewarding substance to substitute for opioids and could lead to cannabis use disorder. However, for medical users, CBD concentration had been set to be higher than THC in order to reduce intoxicating effects of THC. Despite the likelihood of causing cannabis misuse, the compiled data had recommended that cannabis and opioid-antagonist therapy could be an effective approach against OUD. On top of that, this approach could also decrease the risk of cannabis use disorder [31, 32].

### ***C. Obesity***

#### ***General Information:***

Obesity is a complex disease involving excessive fat accumulation in the body. According to the World Health Organization (WHO), obesity is defined as a BMI greater or equal to 30. There are several factors that contribute to obesity. They can be classified into



different types, for instance, behavioral and genetic factors. Examples of behavioral factors are inactivity, dietary patterns, and certain medication use. There are other factors as well, such as surroundings, education, food promotion in the area, etc. Obesity can lead to complications, many medical problems and reduced quality of life. Therefore, addressing this problem as fast as possible is vital for the overall public health. Symptoms of obesity include sleep difficulty, excessive sweating, vulnerability against heat, back pain, joint pain, possible infection in skin folds, fatigue, depression, and dyspnea.

Obesity can be classified into three levels, low risk (BMI is 30.0 to 34.9), moderate risk (BMI is 35.0 to 39.9), and high risk (equal to or greater than 40.0) [33]. There are many causes and risk factors of obesity. Although the causes vary in individuals, obesity occurs when a person's intake calories exceed the calories burned through exercise and daily activities. The body starts to store remaining calories as fat [34].

### *Current Treatments:*

**Dietary changes:** in order to combat obesity, long-term steady weight loss programs are the safest approach. However, there is no best diet for weight loss. Losing weight depends on other factors as well. Thus, one should look for the program that suits them the most. To lose weight effectively, patients might need to work with health professionals, i.e., dietitians, behavioral counselors, or obesity specialists. The most crucial key in weight loss is to cut down on calorie intake. The first step is to analyze the current eating and drinking habits to indicate the problem or the cause of obesity. Then, patients should make a goal they want to achieve; since, motivation is also vital in weight loss. Next, they should devise a program according to the analysis with the help of professionals. Lastly, they have to commit to their plan until they receive a satisfactory result.

**Behavior changes:** like dietary changes, behavior changes' process is to assess current habits and adjust behavior according to individual concerns. The treatment consists of counseling and support groups. Sometimes, the cause of the problem is not from either the environment or surroundings. It could be our body which causes the issue, whether it is anxiety or chemicals in our brains. Hence, communicating with therapists, health professionals or others is a part of fixing patients' issues [35].

**Prescribed medication:** although obesity might be addressed by exercising or changes in diet, some cases cannot be resolved through the same means. If changing diet or other programs do not contribute to any improvement, doctors may recommend weight-loss medications, such as orlistat, phentermine, bupropion, liraglutide, etc. Patients need to be cautious when using these medications; because, not only does it help patients lose weight, but it also has harmful effects when being misused [35, 36].

**Surgery:** in order to receive weight loss surgery or bariatric surgery, individuals need to have high-risk obesity or moderate-risk obesity with serious medical conditions related to weight. They also need to accept the fact that they have to adapt their lifestyles to receive the treatment. After the surgery, the amount of food they can consume and the ability to absorb nutrients and calories are limited [35]. Nevertheless, it is not guaranteed that after the incision patients will definitely lose all the excess weight or the result will remain forever. Besides, bariatric surgery bears some risks as well, dumping syndrome, low blood sugar, malnutrition, vomiting, ulcers, etc. Thus, patients need to be well informed of these risks before agreeing to receive the treatment [37].

### *Therapeutic Properties of Cannabis on Obesity:*

The data was based on self-reported surveys of 41,654 respondents in the National Epidemiologic Study of Alcohol Related Conditions (NESARC) and 9,106 respondents in the National Comorbidity Survey Replication (NCS-R). Out of every participant, 4.0% and 7.3% of the participants in the NESARC and in the NCS-R, respectively, reported having used cannabis at least once in the past 12 months of the recording period. The accumulated data had shown that the pervasiveness of obesity was notably higher in non-cannabis users than in cannabis users. This study also cited other research that explicitly evaluated the association between cannabis and obesity. The results showed significant contrasts between these researches. The first study suggested that subjects with lower BMI tended to have a relation with cannabis use. The second one reported that cannabis use was associated with obesity in female adolescents. The last study showed that the use of cannabis was affiliated with the higher calorie intake, but did not seem to have a connection with a higher BMI [38].

There is not much research related to the specific use of CBD or THC on this topic. However, one study has reported that THC-contained drugs may contribute to weight loss and may have the capacity to be useful as a therapeutic for obesity's treatment and its complications [39].



## *D. Sleep Disorder*

### *General Information:*

Sleep disorder is defined as conditions that alter the way an individual sleeps. It also affects the sleep quality, duration, and the behavior when being awake as well. Not only that sleep disorder can contribute to other medical conditions, but it can also be a sign of symptoms of other mental disorders [40]. Symptoms of sleep disorders include having trouble falling asleep or being awake, being disrupted while sleeping, experiencing an abnormal pattern of breathing while being asleep, having an irregular sleep pattern, etc. [40, 41].

There are countless sleep disorders. Examples of sleep disorders are insomnia (difficulties in falling asleep), sleep apnea (breathing being interrupted while sleeping), circadian rhythm disorder (sleep-wake cycle is desynchronized and disrupts your everyday activities), restless leg syndrome (irresistible urge to move the legs during the attempts of falling asleep), narcolepsy (overwhelming daytime drowsiness). There are many causes that contribute to sleep disorders, and the cause varies from person to person. Despite varieties of causes, the common ground of these disorders is that they interfere with patients' natural sleep cycle and daytime wakefulness. The factors can be classified into medical conditions (cardiac, neurologic, endocrine, pulmonary, gastrointestinal and musculoskeletal), psychological conditions (depression, anxiety, phobias, panic attacks, psychotropic medications), and other factors (aging, trauma, and medications) [42].

### *Current Treatments:*

Non-pharmacological: cognitive-behavioral therapy can be helpful for sleep disorders. The techniques employed include sleep restriction therapy, which limits the amount of time spent in bed to increase desire to sleep, and stimulus control therapy, which aids in changing sleeping habits. Relaxation techniques may be utilized when going to bed. Some hypnotherapists use hypnosis to make patients calm and fall asleep. Changing sleep hygiene can also make a difference. However, non-pharmacological may not be effective in severe sleep disorder

Pharmacological: approved medications include histamine type 1 receptor blockers, benzodiazepines, non-benzodiazepine hypnotics, melatonin receptor agonists, and orexin receptor antagonists. These prescribed sleeping drugs can have negative side effects, such as drowsiness during the day and they can be habit-forming.

Other interventions: losing weight, using continuous positive airway pressure (CPAP), and, in certain cases, surgical treatment can help with sleep apnea. In patients with OSA who experience excessive sleepiness, the medication solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor, can be administered to promote wakefulness. Modafinil, a non-amphetamine stimulant that increases wakefulness, is considered first-line therapy for narcolepsy. Sleep difficulties caused by circadian rhythm anomalies can benefit from light-phase shift therapy. Restless leg syndrome is greatly improved with gabapentin enacarbil, and so sleep disturbance is reduced [42].

### *Therapeutic Properties of Cannabis on Sleep Disorders:*

Sleep issues are frequently stated as a reason for medical cannabis use. ECS is engaged in the maintenance and promotion of sleep through regulating the circadian sleep-wake cycle. In the hamster, the endocannabinoid system had the ability to influence circadian rhythms, and should be examined for effects on circadian rhythm in humans [43]. CB1 receptor distribution in the brain supports a variety of theories about how the ECS could change the suprachiasmatic nucleus (SCN)'s responsiveness to light and affect the circadian rhythm [44].

Chagas et al. (2013) conducted a research on adult male Wistar rats to assess the effects on sleep of acute systemic administration of CBD. 28 rats were divided into 4 groups and received intraperitoneal injections of CBD 2.5 mg/kg, 10 mg/kg, 40 mg/kg or placebo. For four days, sleep recordings were taken during light and dark periods: two days for baseline recording, one day for drug administration, and one day after drug administration. When compared to the placebo group, the overall percentage of sleep increased significantly during the light time of the test day in the groups treated with 10 and 40 mg/kg of CBD. On the post-test day, rapid eye movement (REM) sleep latency increased in the CBD 40 mg/kg group, while it was dramatically reduced in the CBD 10 mg/kg group. Although there was a rise in the time of slow-wave sleep in the CBD 40 mg/kg group, this result did not achieve



statistical significance. This study concluded that systemic acute CBD injection seems to increase total sleep time as well as sleep latency in the light period of administration day [45].

Another research was conducted by Hsiao et al. (2012) on rats. This research aimed at the effect of CBD on anxiety-induced sleep disruptions. The study was employed by repeating combination tests consisting of a 50 minutes open field and a subsequent 10 minutes elevated plus-maze for 4 days to simulate anxiety in the rats. In the later days of the tests, time spent in the center arena of open field and during open arms of the elevated plus-maze was significantly reduced, implying that habituation, which may reduce anxiety-mediated behavioral responses, was not observed. CBD was microinjected into the central nucleus of the amygdala, resulting in increased time spent in the center arena of open field, time spent in the open arms, and reduced frequency of entry into the enclosed arms of elevated plus-maze, demonstrating its anxiolytic impact. After the repeating combination tests, the decrease in non-rapid eye movement (NREM) sleep during the first hour and suppression of REM sleep during 4–10 hours shared similar clinical data in PTSD patients. It was concluded that CBD effectively reduced anxiety-induced REM sleep suppression while having minimal effect on NREM sleep disruption [46].

A study on sleep apnea was conducted by Carley et al. (2002). This study focused on the cannabinoids effect in respiratory stability during sleep by using 11 adult male Sprague-Dawley rats. Polysomnography was used to assess sleep architecture, respiratory pattern, and apnea expression. Animals were monitored after receiving intraperitoneal injections of THC, oleamide, and serotonin, either alone or in combination. Each animal was recorded on exactly 12 occasions in repeated measurements. THC and oleamide both stabilized breathing during all stages of sleep, according to the findings. In NREM and REM sleep, THC reduced apnea index by 42% and 58%, respectively. Oleamide suppressed apnea in a similar way. This finding implied that endocannabinoids play a significant role in autonomic stabilization during sleep. Serotonin-induced worsening of sleep apnea was prevented by oleamide and THC, suggesting that inhibitory coupling between cannabinoids and serotonin receptors may play a role in apnea expression. This study demonstrated that both exogenous and endogenous cannabis decreased sleep-related apnea [47].

Babson et al. (2017) reported that “Preliminary research into cannabis and insomnia suggests that cannabidiol (CBD) may have therapeutic potential for the treatment of insomnia. Delta-9 tetrahydrocannabinol (THC) may decrease sleep latency but could impair sleep quality long-term. Novel studies investigating cannabinoids and obstructive sleep apnea suggest that synthetic cannabinoids such as nabilone and dronabinol may have short-term benefit for sleep apnea due to their modulatory effects on serotonin-mediated apneas. CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness, while nabilone may reduce nightmares associated with PTSD and may improve sleep among patients with chronic pain.” [48].

In rabbits, cats, and people, acute THC treatment reduces REM sleep while increasing slow wave sleep in rabbits, humans, and rats. Chronic administration, on the other hand, has been shown to reduce slow-wave sleep while having variable effects on REM sleep in humans, cats, and squirrel monkeys. When THC was delivered persistently, these findings suggested that tolerance or some other sort of adaptation occurs [49]. However, it was demonstrated that treatment of cultured rat pineals with THC, cannabidiol or cannabinol significantly reduced melatonin biosynthesis [50].

Concluded based on the available evidence, cannabinoids assisted in maintaining and/or promoting sleep and decreasing sleep apnea. The activation of the CB1 receptor caused sleep to be induced [51]. Furthermore, initial work examining specific cannabinoids suggested a potential therapeutic effect of high-dose CBD combined with low-dose THC for sleep [48]. Long term effects of cannabinoids on sleep cannot yet be concluded.

## **E. Cancer**

### **General Information:**

According to the National Cancer Institute, cancer is defined as a great array of related diseases which are characterized by the uncontrolled proliferation of our body's cells. Generally, human cells grow and divide, new cells are formed when the body needs them. Then, when the cells grow to a certain extent or when they are damaged, they die off through the process called apoptosis or cell suicide. After that, new cells come in and take their places. However, in some cases the cells do not die off instead they continue to expand [52]. These extra cells may form tumors, abnormal masses of tissue. Tumors can be classified into benign tumors (not cancerous) and malignant tumors (cancerous). Benign tumors do not spread into or invade other tissues. On the other hand, malignant



tumors or cancerous tumors grow at rapid rates and harm other tissues. Furthermore, malignant tumors can initiate the growth of related tumors in other organs. General signs and symptoms of cancer include anxiety, fatigue, fever, unexplained weight loss, unknown swelling or lumps on the body, chronic pain, unusual bleeding, cough or hoarseness that persists, and so on. However, some patients do not show any kind of symptoms. The only way for them to know that they develop cancer is to do screening tests or a biopsy [53].

Cancer can be divided into four main types based on the origin of it. First type of cancer is carcinoma. Carcinoma develops in the epithelial cells, cells that line the surface of the body. Carcinomas that originate in different epithelial cells have different names, for example, breast cancer, colorectal cancer, prostate cancer, and lung cancer. Second, sarcoma begins in tissues that support and bridge our body, i.e., bone and soft tissues. Examples of sarcomas are undifferentiated pleomorphic sarcoma, liposarcoma, and leiomyosarcoma [54]. Third type of cancer is leukemia. Leukemia is cancer that originates in blood and bone marrow. It develops when healthy blood, specifically, white blood cells, build up and grow uncontrollably. The proliferation of these cells, eventually, inhibits the growth of other normal cells and prevents them from doing what they are supposed to do. There are four major types of leukemia including acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia [55]. Lastly, lymphoma is a cancer that originates in the lymphatic system. There are many kinds of lymphoma. The two major types of lymphoma are Hodgkin's lymphoma and non-Hodgkin's lymphoma [56]. There are many factors that can contribute to cancer. Cancer patients may develop the mutation which can be caused by inheritance from their family, induction from the environment, or result of DNA replication errors (R). Study has suggested that R is responsible for two-third of the development of cancers in humans [57].

### ***Current Treatments:***

**Chemotherapy:** chemotherapy is a drug treatment that is used to treat cancer. By inhibiting the growth of them, cancer cells are, eventually, eliminated. Chemotherapy can be used to treat cancer alone or in combination with other cancer treatments. Although chemotherapy is very effective in treating patients with cancer, it also carries some side effects such as nausea, vomiting, diarrhea, hair loss, fatigue, pain, etc. [58].

**Hormone Therapy:** hormone therapy treats cancer by slowing the proliferation of cancer cells induced by the body's hormones. Cancers that can be treated by this approach include breast cancer and prostate cancer. The most common side effects of hormone therapy are hot flashes (sudden feeling of heat in the upper body), fatigue, weight gain, muscle loss, and hair loss [59].

**Immunotherapy:** immunotherapy is a kind of cancer therapy that enhances the body's immune system in order to fight cancer. After being boosted, the immune system may be able to detect and kill cancer cells which cannot be found before using this treatment. Then, cancer cells will tend to grow slower or stop growing. The side effects of treating cancer patients with immunotherapy are pain, swelling, soreness, redness, itchiness, rash and other flu-like symptoms [60].

**Radiation Therapy:** radiotherapy uses high-powered radiation to kill cancer cells and diminish tumors. Nevertheless, the cancer cells are not immediately eliminated, patients need to receive the treatment several times to damage the DNA of cancer cells enough for them to die. It takes days, or in some cases, weeks to eliminate cancers. The efficacy of radiotherapy also depends on the stage of cancer. Radiation from the treatment does not only kill cancer cells, sometimes it affects healthy cells as well. The side effects include soreness, fatigue, hair loss, loss of appetite, diarrhea, and so on [61].

**Surgery:** surgery for cancer patients is a procedure performed to remove cancer cells in the body. Induced immune system, increased cancer cells shedding, allowed healthy cells to survive, gathered the immune cells to capture cancer cells, caused the target cells and tissues to move to the target sites are all the effects of surgery [62].

**Targeted therapy:** targeted therapy is a cancer treatment in which medications are used to target particular genes and proteins associated with cancer cell growth and maintenance. Targeted therapy can alter the tissue milieu that aids a cancer's growth and maintenance, or it might target cancer-related cells such as blood vessel cells. Targeted therapy is often used in combination with chemotherapy. However, no matter how effective targeted therapy is, it does not always work. Unless the tumor has a target, the treatment will not work. Further, the presence of the target does not ensure that the tumor will respond to the treatment; even if it



responds, the effect may not last indefinitely [63]. The side effects of targeted therapy include rash, dry skin, itching, red or sore cuticles, changes in hair or skin features, and photosensitivity [64].

### *Therapeutic Properties of Cannabis on Cancer:*

Schleider et al. (2018) had evaluated the information compiled as a part of the clinical program involving 2970 cancer patients, who underwent cannabis-related treatment. Out of all participants, 26.7% had reported that they had used cannabis before. The most common types of cancer in this study were breast cancer, lung cancer, pancreatic cancer and colorectal cancer; over half of them were at stage 4. Six months of follow-up passed, and only 1211 participants responded. 95.9% claimed their condition had improved, while 45 patients (3.7 %) stated their condition had worsened [65]. Another research, S. Seltzer et al. (2020), was also conducted to determine the effects of CBD on cancer cells. The result suggested that CBD had potential to be a therapeutic option for cancer therapy in humans, either alone or in combination with other cannabinoids, chemotherapies, and radiation therapy [66].

Gurney et al. (2015) had found the association between chronic cannabis use and the incidence of non-seminoma-type testicular germ cell tumors. Nevertheless, Gurney et al. (2015) had a number of limitations in their review. It was self-reported data without any validation, and the interviewers of the case-control status of the participants could also be biased. Besides, the prevalence of cannabis use in participants could be biased as well. Due to the deficiency in the quality of the studies, there was not enough evidence to suggest that cannabis use could cause testicular cancer [67].

S. Seltzer et al. (2020) reported that, in both cultured cancer cell lines and mouse tumor studies, CBD had exhibited potent anti-proliferative and pro-apoptotic effects on a great range of cancer types. Anti-tumor procedures, depending on the type of tumor, could differ from cell cycle arrest (stopping point in cell cycle where cell stops dividing) to autophagy (mechanism to remove dysfunctional components in the body) to cell death, or a mix of these. Not only that, CBD could also suppress the movement, invasion and neo-vascularization of tumors; however, the required doses of CBD to inhibit the growth of tumor were unknown. There was a risk that comes with CBD use. A study that had done clinical trials in mice and cats indicated that CBD did cause mild hepatotoxicity, thus more research is needed to be done in humans to prove the efficacy and side effects of CBD [66].

### *F. Post-Traumatic Stress Disorder (PTSD)*

#### *General Information:*

PTSD is a disorder that develops in some people who have experienced a shocking, scary, or dangerous event. It is natural to feel afraid during and after a traumatic situation. Fear triggers many split-second changes in the body to help defend against danger or to avoid it. This “fight-or-flight” response is a typical reaction meant to protect a person from harm. Nearly everyone will experience a range of reactions after trauma, yet most people recover from initial symptoms naturally. Those who continue to experience problems may be diagnosed with PTSD [68].

Re-experiencing symptoms: People with these symptoms may have bad dreams, frightening thoughts, or flashbacks about the trauma over and over. Physical symptoms, such as a racing heart or sweating, are also included [68].

Avoidance symptoms: People with avoidance symptoms may avoid objects, places, thoughts, and feelings that are reminders of the traumatic event. Arousal and reactivity symptoms: People with arousal and reactivity symptoms may be easily startled, feel tense, stressed or angry. Arousal symptoms are usually constant, instead of being triggered by things that remind one of the traumatic events.

Cognition and mood symptoms: People with cognition and mood symptoms may have negative thoughts or distorted feelings such as guilt or blame, and be unable to remember key features of the traumatic event. It is natural to have some of these symptoms for a few weeks after a dangerous event. When the symptoms last more than a month, seriously affect one’s ability to function, and are not due to substance use, medical illness, or anything except the event itself, they might be PTSD. Some people with PTSD don’t show any symptoms for weeks or months [68]. PTSD develops in about 1 in 3 people who experience severe trauma. It’s not fully understood why some people develop the condition while others do not. But certain factors appear to make some people more likely to develop PTSD [69]. Types of events that can lead to PTSD include physical or sexual assault, domestic or childhood abuse, war and conflict.



### *Current treatments:*

Medications: sertraline, paroxetine, fluoxetine and venlafaxine received a conditional recommendation for use in the treatment of patients with PTSD. Nevertheless, only SSRIs sertraline (Zoloft) and paroxetine (Paxil) are FDA-approved for the treatment of PTSD. Although SSRIs are generally the most preferable medications used in PTSD treatment, exceptions may occur for patients depending on their individual histories of side effects, responses, comorbidities, and personal preferences [70]. Regarding results of these standard treatments, up to 60% of all patients still have lingering anxiety symptoms. Aside from that, some medications also have significant side effects, which lead to discontinuation among patients.

Psychosocial treatments: cognitive behavior therapy focuses on relationships among attitudes, thoughts, and feelings of patients and aims at changing these undesirable attitudes, thoughts, and feelings, which possibly lead to difficulties in functioning. Another treatment for PTSD is Prolonged Exposure. Patients will gradually approach their memories and feelings related to a traumatic event. This treatment can be highly effective for PTSD since patients possibly learn that traumatic memories and cues are not dangerous and do not have to be avoided [71]. However, it can be costly that some people cannot afford, and also be time-consuming.

### *Therapeutic Properties of Cannabis on PTSD:*

Since ECS is known to have a crucial role in regulating anxiety, stress, and fear, which are related to PTSD symptoms, it is highly likely that influencing the endocannabinoid system could possibly have certain effects on PTSD symptoms. Despite a strong scientific rationale, clinical trials have been rare and all existing research in humans had medium to high risk of bias and significant flaws in methodology and design.

There was a double-blind crossover study of 10 Canadian military personnel who had PTSD and were facing treatment-resistant nightmares. It was found that subjects receiving nabilone, a synthetic form of cannabis that mimics the effects of THC, had a remarkable decrease in nightmares compared to the placebo group. Aside from that, they also had increased scores of general well-being and global improvement. Nonetheless, nabilone is not an extract from an actual plant, and the sample size was fairly small. However, this finding still pointed out that stimulation of cannabinoid receptors possibly has positive effects on some PTSD symptoms, such as nightmares [72].

According to Drnatmed Medical Marijuana Card Colorado (2021), CBD could help empower ECS and improve the quality of their lives. In contrast, there was not a lot of evidence showing that THC helped the symptoms of PTSD since many researchers used nabilone instead of the actual plant. Using the actual plant, therefore, has not been studied too widely just yet. PTSD patients have reported feeling more manic and potentially feeling worse. Using THC products could cause confusion, less bodily control, can trigger anxiety and other adverse effects [73].

## **G. Psychosis**

### *General Information:*

People with psychosis will have certain conditions that affect their mind, where there has been some loss of contact with reality. During a psychotic episode, their thoughts and perceptions are distorted, and they possibly experience difficulty deciding what is real and what is not. Having false beliefs (delusion), disordered movements, odd or illogical thoughts, and hearing or seeing things that are not real (hallucinations) are also included in psychosis symptoms. During a period of psychosis, a person possibly faces positive symptoms or negative symptoms such as anxiety, depression, sleep problems, and social withdrawal [74].

There are many disorders included in psychosis, which are schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, Organic psychosis, Postpartum psychosis, substance-induced psychosis, psychotic depression, bipolar disorder, and dementia. There is no only reason why people develop psychosis. Psychosis may be a symptom of a mental disorder such as bipolar disorder or schizophrenia. Apart from that, sleep deprivation, certain prescription medication, and misuse of alcohol or other drugs can also cause psychosis. All psychiatric conditions also have a strong link to genetic factors. If a person has a relative with mood disorder, the rate of having disorders is 2-3 times higher, and severity of a relative's mood disorder is related to the greater risk of a person's mood disorder.



### *Current treatments:*

Like other disorders, the earlier psychosis is detected, the better outcomes will occur. It is better to be treated at an early stage since the illness has not developed yet.

Individual or group psychotherapy: this therapy is specific to each individuals' needs. It encourages patients to manage illness and wellness, build ability to tackle problems, and be flexible.

Medication (pharmacotherapy): antipsychotic medication will alter the brain's chemicals, which include Dopamine. To determine what medicine and dose have to be used, individuals' needs have to be taken into account. Despite possibly having an immediate calming effect or being able to sleep, Patients taking antipsychotic medication usually take several weeks to have symptoms, such as hallucinations, reduced. Nevertheless, Antipsychotics have serious side effects including perturbations in motor systems, blurred vision, stiffness and shakiness. Moreover, Antipsychotics also have only a moderate response rate, around 40-50%.

### *Therapeutic Properties of Cannabis on Psychosis:*

There are laboratory rodents and human studies suggesting that cannabinoids have an ability to prevent human experimental psychosis and psychotic-like symptoms induced by high doses of THC. Subsequent studies observing animal models and healthy individuals also suggested that CBD has antipsychotic effects. In addition, CBD was also effective in open case reports and clinical trials in patients who have schizophrenia, one type of psychosis, with a remarkable safety profile [75]. However, there are other past papers supporting cannabis use as a contributory cause of psychosis. These longitudinal studies of adolescents and young adults showed the relations between the risk of being diagnosed with a psychosis or having psychosis symptoms and self-reported cannabis use. Evidence was assessed with the aim to assure the biological plausibility of a contributory causal relation. Referring to six longitudinal studies, in which confounders such as personal characteristics and other drug use were controlled, in 5 countries, regular cannabis use seemed to be able to predict an increased risk of being diagnosed with a psychosis or having psychosis symptoms. A contributory causal relation was biologically plausible since the cannabinoid system interacts with the dopamine neurotransmitter systems, which would also be disturbed when a person has psychosis. Therefore, it was highly likely that cannabis use precipitated psychosis in individuals who were vulnerable because of a personal or family history of schizophrenia [76].

Referring to the current studies, including animal, human experimental, clinical studies, which examined the psychosis model, psychotic symptoms, or psychotic disorders and the use of CBD, evidence from these studies showed that CBD has potential for antipsychotic treatment [77]. However, there was an association between cannabis use and an increased risk of developing psychosis. Therefore, further research has to be done to identify the factors that underlie individuals' risks to develop psychosis and clarify the biological mechanism underlying this risk [78].

## **H. Epilepsy**

### *General Information:*

Epilepsy is one of the most common serious brain disorders, which entail a burden in seizure-related disability, stigma, costs, comorbidities, and mortality [79, 80]. It can occur at all ages, and potentially have numerous possible causes and symptoms [80]. When brain activity becomes abnormal, seizure can occur; however, having a single seizure does not mean that a person has epilepsy. Symptoms depend on the type of seizure, and different mutations in one gene can lead to different types of epileptic syndrome.

Signs and symptoms of epilepsy are various and can be divided into several types including refractory epilepsy, photosensitive epilepsy, benign rolandic epilepsy, juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, abdominal epilepsy, absence seizures, and temporal lobe seizures. Causes of epilepsy are not completely known. Some people with no clear cause of epilepsy potentially have a genetic form of epilepsy. However, relations between genes and seizures are not exactly understood, and genetic testing is not available yet for many forms of epilepsy. Infections of the brain, change in brain structure, head injuries, stroke and other conditions such as Alzheimer's disease or other conditions that affect brain function can also cause seizures.

### *Current treatments:*

Pharmacological treatment: treatment decisions should be decided individually, and the risk-benefit ratio of each option should be taken into account. There are more than 20 antiepileptic drugs that are available to treat epilepsy in adults. Each drug choice mainly



relies on effectiveness and efficacy for the individual's seizure type. Nevertheless, other personal factors including gender, age, childbearing potential, and comorbidities also have to be considered [81]. Nevertheless, epilepsy cannot be controlled in 20–30% of patients, and patients with drug-resistant epilepsy often have serious comorbidity, including injury, depression, anxiety, and increased mortality [82].

Surgical treatment: when two well-chosen and tolerated medications do not work, a presurgical evaluation should be arranged [83, 84]. Patients should be identified early in the evaluation and treatment in order to undergo surgery. This treatment is favorable for those who have medial temporal lobe epilepsy and partial seizures related to selected lesional pathology [83]. If the brain region, where the seizures arise, is identified, this region can be removed with a low risk of disabling neurological deficits [84].

### *Therapeutic Properties of Cannabis on Epilepsy:*

Gaston et al. (2018) presented data from two trials, open-label expanded access programs (EAPs) and randomized placebo-controlled trials (RCTs), using highly purified oral preparation of CBD. According to the data from EAPs, a large number of patients with several types of treatment-refractory epilepsy had a significant improvement in seizure frequency. RCTs, which was recently approved by the FDA for treatment of epilepsy, showed significant reduction of seizure when compared to patients with Dravet syndrome and Lennox-Gastaut syndrome who received placebo [85]. Nevertheless, drug-drug interaction, which can cause adverse effects, can occur with highly purified CBD. Diarrhea and sedation are the most common side effects. Apart from that, patients also experience an increased incidence of aspartate aminotransferase and alanine aminotransferase whilst taking CBD [85].

Even though cannabis and THC are anticonvulsant in most animal models, there are some cases of healthy animals, where CBD and THC can be proconvulsant as well. The antiepileptic mechanisms of CBD are not totally understood, but effects on the equilibrative nucleoside transporter are possibly included. However, despite having anti-inflammatory and neuroprotective effects, studies of CBD in human epilepsy are still small and methodologically limited, hence being inconclusive. High-ratio CBD:THC medical cannabis is suggested to have claimed efficacy by recent studies, but these reports are not controlled. In other words, the efficacy of pure CBD in chronic patients and for epilepsy is not well understood because of the lack of data from well-powered, double-blind randomized, and controlled studies [86].

## **I. Traumatic Brain Injury (TBI)**

### *General information:*

TBI is defined as a physical injury to the brain tissue that temporarily or permanently alters brain function. Various types of structural damage can be caused by head injuries. Mechanism and force play a role in determining whether structural changes will be gross or microscopic [87]. People with TBI possibly experience confusion, altered level of consciousness, seizure, coma, and focal sensory or motor neurologic deficit. Moreover, TBI is a common cause of death as well as a major cause of epilepsy.

Types of TBI can be classified by many criteria. One of them is physical mechanism classification, which considers whether the head strikes an object and the brain moves within the skull. The specific forces at specific magnitude and direction of each type are potentially able to predict patterns, types, and severity of the injuries [88]. There are 4 types of TBI, which are concussions (minor brain injury), brain contusions (a bruise of the brain tissue), penetrating brain injuries (when some type of object pierces through the skull), and anoxic brain injuries (when there is insufficient oxygen for the brain to operate properly). Causes of TBI depend on various factors, including age, geographic region, and socioeconomic factors. Road traffic injuries (RTI) also relate to the global incidence of TBI. In high-income countries (HICs), the most frequent causes of TBI are RTI and falls, which is the primary cause in the elderly. Nonetheless, younger people, whose age is between 28.8 and 33.1, in less wealthy countries have a higher rate of experiencing TBI [89]. Other incidents, such as violence, sport injuries, explosive blasts and other combat injuries, also can cause TBI.

### *Current treatments:*

Immediate treatment after injury: in moderate and severe TBI patients, it is vital to ensure that they have sufficient oxygen and adequate blood supply. Maintaining blood pressure and preventing further head and neck injuries are also important. When patients arrive at the emergency room or intensive care unit, minimizing secondary damage from inflammation, inadequate oxygen supply, and bleeding. Some medications including diuretics, anti-seizure drugs, and coma-inducing drugs are sometimes needed.



Treatment for mild TBI: mild TBI, including concussion from sports accidents, usually require only rest and pain relievers to reduce headache with no other treatments. Patients should limit physical activities and difficult cognitive tasks, and focus on brain rest soon after injury. However, close monitoring at home is also important to notice any persistent, worsening, or new symptoms.

### ***Therapeutic Properties of Cannabis on TBI:***

Even though, nowadays, no pharmacological agent presents therapeutic efficacy of cannabis for TBI, medical cannabis may become one of the treatment options thanks to recent legalization efforts and increasing popularity of it. In pre-clinical TBI research, it was suggested that cannabinoids have neuroprotective and psychotherapeutic properties; however, recreational cannabis seemed to have adverse effects. With regards to observational studies, it appeared to be those patients with TBI use both medical and recreational cannabis to treat their symptoms [90]. Beside this, there was a study using a weight drop mild TBI mouse model to examine the effects of 10% CBD oil on sensorial and neuropsychiatric dysfunctions, which are related to mild TBI through biomolecular and behavioral approaches. The result suggested that CBD oral treatment partially normalized the cortical biochemical changes and restored the change in mouse's behaviors. This study pointed out that CBD can possibly be a pharmacological tool to ameliorate neurological dysfunctions caused by the trauma, and certain brain modifications possibly play a role on behavioral phenotype associated with TBI [91]. Nevertheless, the empirical evidence of cannabis effects on TBI patients is still sparse and limited [90].

The endocannabinoid system plays a role in regulating diverse arrays of physiological processes and unexpectedly has considerable potential targets for the treatment of various TBI pathologies. Increase of endocannabinoids in the brain to pathogenic events showed that this system has an influence in compensatory repair mechanisms. There are preclinical studies examining the therapeutic properties of cannabinoids and manipulation of its system to improve TBI pathology. Cellular and molecular hallmarks of TBI pathology, including neuroinflammation, cell death, and cerebrovascular breakdown, could be modulated by CB1 and CB2 receptors, and their endogenous ligands. Endocannabinoid system also has association with TBI-induced behavioral deficits, such as seizures, anxiety, and neurological motor impairments [92]. However, more research has to be done for better understanding with regard to promising classes of compounds, such as plant-derived and synthetic phytocannabinoids, and their non-cannabinoid receptor targets.

### ***J. Parkinson's Disease (PD)***

#### ***General information:***

Parkinson's Disease (PD) is a motor system disorder and the most common neurodegenerative movement disorder. Currently, this disease is chronic and incurable, leading to progressive degeneration. There are 4 primary symptoms of PD, which are tremor, rigidity, bradykinesia, and postural instability. Elderly, whose age is over 60, are usually affected by PD, and these symptoms possibly cause difficulty with simple or daily tasks.

There is no existing test that can conclusively identify what type of parkinsonism patients are experiencing. Years may elapse between facing the first symptoms and being informed of a definitive diagnosis of a specific type in some patients. In some cases, patients potentially have more than one type of parkinsonism. Forms of parkinsonism are divided into 4 main types, which are idiopathic Parkinson's disease, arteriosclerotic parkinsonism, drug-induced parkinsonism, and other types of parkinsonism. The causes of PD are still generally unknown; however, it is currently believed that a small proportion of all cases of PD are caused by major gene mutations, and non-genetic factors also play a part, potentially interacting with susceptibility genes, in most cases [93]. Less than 5% of PD's forms are monogenic, such as caused by single genes' mutations, and there are plenty of genes that cause atypical forms of parkinsonism. In contrast, a multifactorial nature, and a number of environmental factors also have associations with idiopathic PD. Experiencing pesticides and a head injury show genuine risk factors. Other factors including smoking and consuming alcohol and coffee are not yet considered risk factors, and most of their cause-effect relationships have not been illustrated. Nevertheless, the respective disease mechanisms are still not fully understood, and the underlying functional genetic variants have not been identified at the present [94].

#### ***Current treatments:***

There is no cure for PD, but treatments can improve symptoms. All patients' treatment is symptomatic, and focused on both improvement in motor and non-motor signs and symptoms. There are also no disease-modifying pharmacologic treatments available



for PD's patients. For initial motor symptoms, it can typically be treated by using Dopamine-based therapies, and non-dopaminergic approaches, including cholinesterase inhibitors for cognition, are required for nonmotor symptoms. Rehabilitative therapy and exercise are a supplement for pharmacologic treatments. In those who experience medical-resistant tremor, worsening symptoms, and functional impairments when the medication wears off, treatments such as deep brain stimulation and levodopa-carbidopa enteral suspension could have benefits for them [95]. Nevertheless, levodopa treatment, which is currently considered the most effective medication for PD, causes a type of long-term dyskinesias, l-DOPA-induced dyskinesias (LIDs) [96]. Even if the aim of current treatments is to improve functional capacity of the patients, they are not able to modify the progression of the neurodegenerative process [97].

### *Therapeutic Properties of Cannabis on Parkinson's Disease:*

Although cannabis has been used for thousands of years for medical purposes, effects of cannabis use on PD, both negative and positive, are generally unknown. There was an anonymous web-based survey collecting demographic and cannabis use information. This survey used standardized questionnaires to evaluate neurological function, balance, fatigue, and physical activity participation, and also used analysis of variance and chi-square tests for the analysis. The survey was visited 801 times, and 76% of 595 participants reported PD. Current users reported lower levels of disability, especially in domains of mood, memory, and fatigue. In addition, they also suggested that cannabis had high efficacy, and 59% of them experienced the reduction in prescription medication since beginning cannabis use. Currently, cannabis users are younger and less likely to be diagnosed with obesity. In conclusion, it was highly likely that cannabis possibly has positive effects on mood, memory, and fatigue in patients with PD. More research is needed to be done in order to determine their association, effects of cannabis use, and its long-term benefits in people with PD [98].

CBD has been shown to have compensatory impacts on the endocannabinoid system. Reserpine and other PD models were also affected by CBD, as a neuromodulator and neuroprotector. While the observation of CBD-induced neuroprotection in animal models of PD has been attributed to the activation of the CB1 receptors, recent research conducted at a molecular level suggested that CBD was only able to activate other receptors, including CB2 and TRPV-1. Consequently, it causes a variety of biochemical, molecular, and behavioral effects since there are a broad range of receptors being able to activate in the CNS. Thanks to these findings, a new line of scientific inquiry is opened into the effect of CBD at the neural communication level [99].

### *K. Alzheimer's disease (AD)*

#### *General information:*

Alzheimer's disease (AD) is a non-reversible and age-related brain disorder that develops over a period of time. It involves parts of the brain that control memory, thought, and language. First symptoms usually first appear when a person is in their mid-60s. The most prevalent symptom is difficulty in remembering recent events. Moreover, it can seriously impact patients' ability to do daily tasks, which makes some patients dependent.

Alzheimer's symptoms can be classified by considering the severity of them, and there are 3 main types, mild Alzheimer's, moderate Alzheimer's, and severe Alzheimer's, which can possibly be considered stages of AD since it usually progresses to a more severe form. People with mild Alzheimer's begin to have cognitive impairment, which causes difficulties in remembering daily tasks. Since these symptoms are not very serious, patients can still do the same tasks, but require longer time.

Symptoms of moderate Alzheimer's are more severe due to more neuronal damage. They will be more dependent and confused because of the amount of memory loss. Although they are still physically strong, routine tasks cannot be done since sensory processing of their thoughts are taken over by the delusion. Patients with severe Alzheimer's are generally bedridden and are hardly able to communicate. Their brain cells start dying because of the plaques and tangles, which leads to shrinkage of brain tissue [100]. It is believed that deposition of beta-amyloid protein and hyperphosphorylation of intraneuronal tau protein, which lead to conditions including synaptic degradation, neuronal loss, brain circuit disruption, is associated with the occurrence of AD [101]. Apart from this, genetic factors are currently believed to play an important role in the risks of developing AD. Early-onset familial AD can occur from rare mutations in at least 3 genes. The major determinant of risk in late-onset familial AD and general population is a common polymorphism in the apolipoprotein E gene. Even though environmental variables possibly influence disease expression, aging is still the major risk factor. There are also some pathogenic factors that are directly associated with aging, such as mutations in messenger RNA. Thanks to more understanding of the pathogenic mechanism of AD, older theories, including those suggesting



aluminum as one factor affecting the pathogenesis of AD are discarded [102]. However, there is another hypothesis suggesting that mild cognitive impairment and Alzheimer's disease are mainly caused by copper toxicity. Inorganic copper derived from drinking water and copper supplements may be toxic as it probably penetrates the blood brain barrier [103].

### **Current treatments:**

Acetylcholinesterase inhibitors are used for AD treatment; although it can improve cognitive, functional, and behavioural symptoms, its effects on AD pathogenesis is not yet understood. There are also other possibly disease modifying treatments, such as amyloid- $\beta$ -peptide vaccination, secretase inhibitors, and anti-inflammatory agents [104]. Since it was found that the deposition of beta-amyloid protein, produced in huge quantities in the brain, is thought to be toxic, current treatment development has focused on it. Nevertheless, despite being associated with reduction in amyloid, amyloid oriented therapies focusing on patients with mild cognitive impairment did not result in successful results. At the present, there are attempts to use these therapies for patients with very early symptoms or considered at risk by genetics and scanning brain amyloid PET scan [101].

### **Therapeutic Properties of Cannabis on Alzheimer's Disease:**

There were studies suggesting that CBD components are potentially useful for treating and preventing AD since they were able to suppress the main causal factors of AD. In addition, using CBD altogether with THC could provide better results than using only CBD or THC. According to *in vitro* studies, CBD has demonstrated neuroprotective, anti-inflammatory, and antioxidant properties. Consequently, it was examined as a possible multifunctional treatment for AD. Other *in vivo* studies, which used pharmacological and transgenic animal models for AD, showed that CBD was able to promote neurogenesis and reduce reactive gliosis and the neuroinflammatory response. Moreover, in an AD rodent model, CBD also had the ability to reverse and prevent the development of cognitive deficits. Surprisingly, therapies using CBD with THC demonstrated that CBD is able to antagonize the psychoactive effects related to THC. Like the aforementioned studies, CBD-THC combinations seemed to have better treatment results than using only CBD and THC. Further research has to be done to address the long-term impacts of CBD and examine mechanisms included in their therapeutic effects [105].

The underlying molecular mechanism of CBD, which is considered a therapeutic candidate for neurodegenerative diseases, was comprehensively clarified. CBD not only prevents glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) hyperphosphorylation, which is caused by A $\beta$ , but also indirectly acts as an endogenous cannabinoid receptor agonist to exert its neuroprotective effects. Furthermore, different signal transduction pathways are promoted, mediated indirectly by cannabinoid receptors, by CBD [106].

## **DISCUSSION**

Certainly, there is much evidence regarding the therapeutic effect of cannabis. Cannabis has been shown to be very useful in reducing chronic pain in various diseases, except in Crohn's disease. The majority of trials involved the use of 1:1 ratio of CBD and THC for the treatment of severe chronic pain. Pregnant women should exercise caution when taking cannabis-related medications, as this increases the risk of neonatal illness or death. OUD could also be remedied using cannabis with high CBD and low THC because these compounds can be used to relieve pain, which is often the purpose of opioids users. On the other hand, higher amounts of THC, which is a rewarding chemical, could replace opioids, leading to cannabis use disorder. Cannabis effect on obesity is still inconclusive as one study concluded that cannabis use was related to higher calories intake, but another suggested THC might aid weight loss and had the potential to be used as a therapy for obesity. Preliminary research suggested that cannabis was beneficial for sleep disorders, despite most studies being conducted on animals. Even though THC can decrease sleep latency, high CBD and low THC was recommended since THC's long-term effect is unclear. It was also determined that cannabinoids reduced sleep apnea. The topic of cancer treatment by cannabis is still controversial. Results of different studies contradict one another. Some research had a deficiency in its quality, resulting in inconclusive results. A study also suggested, with sparse evidence, that cannabis might increase the risk of testicular cancer. Another study on cancer indicated that CBD caused mild hepatotoxicity. CBD was demonstrated to improve quality of life in PTSD patients. Research using nabilone, a synthetic form of THC, showed a decrease in nightmares for PTSD patients. Even so, THC's actual effect may be different from nabilone and another study reported of participants feeling more manic and likely worse while using THC. CBD appeared to have an antipsychotic impact in animal models and healthy people, according to studies. Another past publication, on the other hand, suggested cannabis use as a contributory cause of psychosis in families with mental health history. This could be a result from THC as it can induce psychotic-like symptoms. The



efficacy of cannabis in epilepsy patients is still not clear due to lack of data but there was evidence that diarrhea and sedation are the most common side effects. Results concerning TBI showed that CBD could possibly treat neurological dysfunctions brought on by trauma, but the empirical evidence is still sparse. Cannabis' remedial effect on PD is still undeterminable but it may have beneficial effects on mood, memory, and exhaustion in PD patients. Regarding AD, research showed evidence that cannabis may treat the disease by using a combination of THC and CBD. Nonetheless, the long-term impacts on this disease could not be addressed.

The topic about cannabis dosage is still debatable. Most studies suggested that there are no benefits from high doses of THC, since high doses of THC come with risks including cognitive impairment, psychosis risk, tolerance to cannabinoids, and endocannabinoid alteration. In contrast, high doses of CBD were required for the beneficial effects. CBD should be adjusted to greater concentration than THC in order to minimize THC's intoxicating effects. Cardiovascular illness, acute pancreatitis, cannabis hyperemesis syndrome, and industrial injuries can all be exacerbated by high THC levels. Anyhow, the standard dosage for each medical condition was not concluded.

It can also be seen that research on THC use for each disease is significantly lower than CBD. Most research and trials are focused on the use of CBD possibly due to the psychotic properties of THC. Although the majority might think THC consumption is for recreational purposes, many studies concluded that THC exhibits a therapeutic effect on certain medical conditions. While risks of THC use are great, the risks can be minimized by combining with CBD. Hence, more research on THC therapeutic properties should be conducted.

Many barriers still exist as an obstacle to research on cannabis. Most research on cannabis could not be done at a large scale due to many legal issues. To illustrate, the Controlled Substances Act (CSA) of 1970 in the USA categorized cannabis and THC as Schedule 1 drugs, which refers to a drug with no accepted medical use and a high potential for abuse. These legal barriers make it difficult to conduct research and clinical trials on humans. Findings from animal studies cannot conclude the effect of cannabis on humans. Should cannabis be completely legal for medical purposes, more studies would be permitted. So far, there are various gaps in the information we have, for example, the standard dosing and the long-term side effects. Much more research and clinical trials are essential to discover all of cannabis' therapeutic properties.

## CONCLUSION

To summarize, there is substantial evidence that cannabis use positively affects the alleviation of chronic pain, OUD, sleeping disorders, and Alzheimer's disease. Favorable effects on PTSD, psychosis, and TBI have been found only in CBD. There is not enough evidence to conclude that cannabis use has beneficial effects on obesity, cancer, epilepsy, and Parkinson's disease. Nevertheless, absence of evidence does not necessarily imply no therapeutic effect. Risks of cannabis consumption for these conditions include cannabis use disorder, pregnancy complications, mild hepatotoxicity, cause of psychosis, drug-drug interaction, diarrhea, and sedation. Most studies recommended that using a combination of high portion CBD and low portion THC would maximize benefits and minimize the risks and no study suggested that high doses of THC is beneficial. Current information and empirical findings of cannabis are still insufficient, therefore, more research needs to be conducted to fully understand cannabis' properties. We hope this review will provide empirical data that can improve the understanding of medical cannabis.

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