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Review Article

Cannabis in the Treatment of Mental Health

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Abstract

Cannabis is a commonly used psychoactive substance. An estimated 183 million people used it in 2016. A lot has been said of the negative effects of cannabis on brain function and mental health. This review serves to highlight some of the literature on the research in to the positive effects of cannabis on mental health. A brief explanation of the neurobiology of cannabis and the workings of the endogenous cannabinoid system are included to aid understanding. The possible uses of cannabis looked in to are - pain management, anxiety, mood disorders, psychoses, insomnia, suicides, aggression, Alzheimer's, and ADHD. Some future research directions of note are comparative studies looking at the benefits of cannabis vs. existing pharmacological treatments, the effectiveness of cannabidiol, as well as longitudinal studies looking at the long-term effectiveness and detrimental effects of controlled cannabis use for therapeutic purposes.

Keywords: Cannabis; Tetrahydrocannabinol; Cannabidiol; Mental Health; Cannabis for Therapeutic Use

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; BD: Bipolar Disorder; CBD: Cannabidiol;CTP: Cannabis for Therapeutic Purposes; CUD: Cannabis Use Disorder; PTSD: Post Traumatic Stress Disorder; SAD: Social Anxiety Disorder; THC: delta-9-tetrahydrocannabinol.

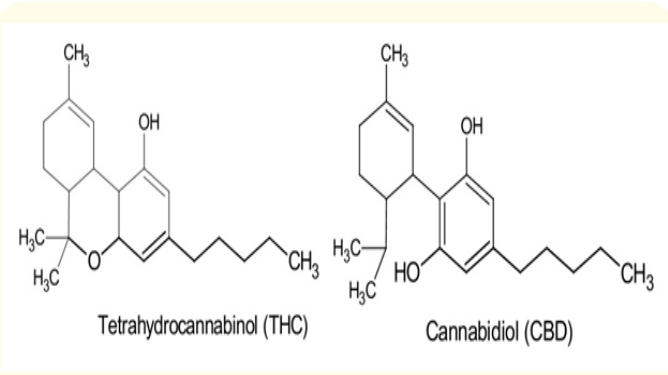
Background

Cannabis is a genus of flowering plant in the Cannabaceae family. Three species of Cannabis are commonly used for consumption - cannabis sativa, cannabis indica, and cannabis ruderalis. The genus is indigenous to central Asia and the Indian subcontinent. Cannabis or Marijuana is one of the world's most widely used psychoactive substances. According to the United Nations World Drug Report [1], an estimated 183 million people around the world - more than 3.8% of the world's population aged between 15 and 64, use it.

The use of cannabis as a method of treatment of mental disorders is a concept that is gathering interest [2,3] but is also fraught with controversy, such as the relationship between cannabis intake and the increased risk of developing a psychotic illness later in life [4,5]. Some researchers have questioned the medical usage of marijuana [6]. Nevertheless, interest in its applicability in treating both physical and psychological conditions is gaining momentum. The potential medicinal properties of marijuana and its components have been the subject of research and heated debate for decades. Over the last few years, landmark changes have happened. An example of this is the US Food and Drug Administration approving THC-based medications, such as dronabinol (Marinol®) and nabilone (Cesamet®), prescribed in pill form for the treatment of nausea in patients undergoing cancer chemotherapy and to stimulate appetite in patients with wasting syndrome due to AIDS.

Neurobiology

Marijuana contains more than 400 chemical compounds, including over 100 distinct cannabinoid compounds and several of them have proven to have psychoactive effects [7]. The primary psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC) [8]. Other plant cannabinoids include delta-8-tetrahydrocannabinol; cannabinol; and cannabidiol (CBD); CBD is the second major psychoactive constituent of cannabis [9]. Currently, the two main cannabinoids from the marijuana plant that are of medical interest are THC (Tetra Hydro Cannabinol) and CBD (Cannabidiol).



THC & CBD molecular structures [Digital image]. (2013, May).

The endogenous cannabinoid system consists of two types of G-protein-coupled receptors: cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors. CB1 receptors are the most abundant in the brain, in regions like the hippocampus, prefrontal cortex, anterior cingulate, basal ganglia, cerebellum, cortex, thalamus, hypothalamus, and amygdala, and these areas are involved in cognition and in patients with psychosis.

CB2 receptors predominate on immune cells. Activation of CB1 receptors mediate the behavioural and physiological effects of both endogenous and exogenous cannabinoids in the brain [10]. CB1 receptors modulate neurotransmitter release so that equilibrium is maintained by preventing excessive neuronal activity in the CNS [11]. CB1 receptors are localized on presynaptic neuron terminals on both inhibitory and excitatory neurons but it is the inhibitory neurons that are thought to mediate most of the effects of cannabinoids [12]. In addition, cannabinoids interact with the dopaminergic system. THC is a partial agonist at the CB1 receptors, where it has modest affinity.

In contrast, CBD shows very little affinity for CB1 receptors. Cannabinoids produce an increase in the dopaminergic activity in the mesolimbic reward pathway and this is responsible for the abusive property of the drug and increases in positive psychotic symptoms induced by THC [13].

Current Research on Negative Effects

There has been substantial research on the negative effects of cannabis on mental, as well as, physical health. Certain areas are - psychosis [14,15] depression [4,16,17] increased chance of vehicular accidents [18], poor educational performance [19], cancer, because of cancerogenic mutagens in cannabis that affect the lungs [20].

However, with growing interest in its positive effects, this paper looks at the use of Cannabis for the treatment and improvement of certain mental health conditions. For this purpose, areas of research documented are use of cannabis in anxiety, epilepsy, PTSD, depression, psychosis, and ADHD.

Ancient Uses

According to Chinese legend, in 2737 BCE, Emperor Shen Neng of China used cannabis as medicine. In 1213 BCE, Egyptians used cannabis for glaucoma, inflammation, and enemas, and in 1000 BCE, bhang a drink made of cannabis and milk, was used in India as an aesthetic [21]. In recent years, there has been renewed interest in the potential medicinal properties of marijuana and its components.

Positive uses at a glance

Limited research has shown benefits of THC for enhancing appetite in those with AIDS and Alzheimer's [22]. In some clinical trials of THC and cannabis, a beneficial effect on spasticity and tremors caused by multiple sclerosis or spinal cord injury was noted [23]. There is also some research to indicate a therapeutic response of cannabis on Tourette's syndrome [24].

Cannabis can reduce intraocular pressure, and this effect has been tried on glaucoma [25]. Recent research has reported that CBD shows promise for the treatment of seizure disorders, especially drug resistant childhood epilepsy [26]. Since CBD does not have the rewarding properties of THC, there is no cause for concern about addiction in youngsters. A CBD based liquid medication called Epidiolex has been tested in the US for the treatment of two forms of severe childhood epilepsy, Dravet syndrome, and Lennox-Gastaut syndrome.

Medical Marijuana

The term *medical marijuana* refers to using the whole, unprocessed marijuana plant or its basic extracts to treat symptoms of illness and other conditions [27].

A large study by [28] with 433 participants drawn from an abstinence-based substance use disorder program saw 15% using marijuana to treat pain. In another study, [29] looked at self-selected CTP (Cannabis for Therapeutic Purposes) program applicants and found a reduced use of other substances from adolescence to adulthood. This led them to suggest that CTP use may have been protective against development of problematic use of other substances. There is some evidence for cannabis serving as an "exit drug", with the potential to facilitate reductions in the use of other substances [30,31]. According to this perspective, cannabis serves a harm-reducing role by substituting for potentially more dangerous substances such as alcohol [32] and opiates [33]. [34] examined cannabis substitution for alcohol and noted that cannabis met nearly all the criteria required for consideration as a substitute therapy. This is one area that cannabis could be used as treatment. However, there is the risk that CTP can convert to non-medical cannabis use or cannabis abuse.

Possible uses of CTP

Pain relief

[35] looked at medical use of cannabis in their cross-sectional study in Australia. The highest percentage of use was for treating chronic pain, at 57%. Users targeted pain from illnesses such as fibromyalgia, spinal injuries, arthritis, neuralgia, neuropathy, migraine, etc. In a Canadian study by [3], CTP users were found to be treating chronic pain from spinal and non-spinal injuries caused by muscle spasms. Users were also treating inflammation from arthritic pain. [27] found 97% of respondents used cannabis primarily to treat chronic pain in a survey of 100 patients. They reported that average pain improvement on a 0-10 pen scale was 5.0 (from 7.8 to 2.8), which translated to 64% relative decrease in average pain.

Anxiolytic Effects

[27] found that half of all respondents reported relief from anxiety. The [35] cross-sectional study reported a drop-in symptom of anxiety with cannabis use in 30% of participants, which returned upon cessation of use. It should be noted that cannabis is characterized by both anxiolytic and anxiogenic properties [36] and awareness of the anxiogenic effects of cannabis withdrawal may be important when evaluating or treating anxiety, as symptoms may be associated with emergent symptoms of withdrawal associated with fluctuations in levels and frequency of use.

Amongst the different types of anxiety disorders, research has looked into treatment of Social Anxiety Disorder (SAD) and Post-Traumatic Stress Disorder (PTSD). Socially anxious individuals are more likely than individuals with other anxiety disorders to use cannabis as a form of relief [37].

Research has shown that administration of CBD is associated with decreased subjective anxiety among SAD patients [38,39] and decreased cognitive impairment, negative evaluations, and anxiety in a simulated public speaking task [40]. [41] reported better physical functioning in those with comorbid SAD and Cannabis Use Disorder (CUD) versus those with SAD alone. Given these findings there is a potential therapeutic application for cannabinoids in SAD.

CTP has been recognized as beneficial for the treatment of symptoms associated with PTSD. Studies show that CTP users with PTSD use cannabis to facilitate sleep and cope with negative affect [42]. The administration of oral THC has shown these effects as well in treatment-resistant PTSD patients [43]. It should be noted that those using CTP for PTSD can develop CUD and experience diminished benefit from traditional PTSD treatment [44] and heightened withdrawal when quitting [45].

Mood Disorders

Moreau, in 1845, reported the antidepressant activity of CTP. In recent years, several studies have reported improved mood with CTP in a number of patients with depression and other comorbid medical conditions [46] Harris., *et al.* 2000; [47,48] In the [35] study, 30% of participants reported relief from depression. Of the 698 CTP users in the [3] study, 394 reported relief from depressive symptoms. It should be noted that there are contradictory reports of increased risk of depression in those with non-medical cannabis use [17,49,50].

There are some reports of using cannabis to treat symptoms of bipolar disorders (both manic and depressive symptoms) [51,52]. However, more research is needed before it can be concluded that CTP is beneficial for mood disorders.

Psychoses

Research has shown evidence suggesting earlier onset of psychosis for those using cannabis as compared to non-users [11] and an influence of cannabis use on those with genetic vulnerability to psychosis [53].

One mechanism is to do with THC. It increases dopamine release in the brain and this relates to the dopamine hypothesis for schizophrenia.

Despite the above, cannabis is used to alleviate psychotic symptoms. THC is psychotomimetic, but CBD is not and has shown antipsychotic properties which may counteract the effects of THC [54,55] CUD is especially common in younger and first-episode psychosis patients [56], so it may be possible that individuals at risk for developing psychosis use cannabis as a means of alleviating prodromal symptoms [4].

Insomnia

Studies on cannabis and sleep were first conducted in the 1970s [57], and showed low doses of THC increased deep sleep. However, this effect disappeared after repeated use and with higher doses. Recent research by [27] found that 47% of participants reported relief from insomnia. [58] found that 56% of CTP users in their study in California were using it to treat insomnia. When THC was stopped, a rebound effect in REM sleep was found with reduced sleep time and increased time to fall asleep.

Suicides

Reports on suicides are anecdotal and contradictory. Some studies suggest a decreased rate of suicide (Anderson., *et al.* 2014; Rylander., *et al.* 2014), while other studies indicate an association between non-medical cannabis use and subsequent suicidal ideation and attempts even after controlling for potential confounds [59,60].

Aggression

There have been reports of reduced aggression in cannabis users [61,62] because of its sedative nature. However, whether there is a possible use in aggressive patients is inconclusive due to the lack of research [7].

Alzheimer's disease

A preclinical study by [63] found very small doses of THC can slow down the production of β-amyloid proteins, thought to be a key contributor to the progression of Alzheimer's. In addition, low doses of THC can enhance mitochondria function, which could be a potential therapeutic treatment option.

ADHD

Cannabinoids interact with the brain's dopamine management systems, increasing the availability of dopamine. Limited studies have suggested that cannabis can improve cognitive ability and impulse control [64]. Stimulant medications such as Ritalin and Adderall help correct dopamine levels but have side effects. These effects together point to the use of cannabis as a potential treatment option for ADHD.

Limitations and Future Directions

A large number of the studies reviewed here were cross-sectional. Many were of low to medium methodological quality. Some areas did not have a lot of research to review. In addition, some of the research is older in nature dating as far back as the 1970s.

Looking ahead, a promising area that needs more research is the effects of CBD. Unlike THC, CBD does not lead to a "high". The research reviewed above shows the positive effects CBD can have on a variety of symptoms and illnesses. As noted above, CTP users report anxiolytic effects and there is literature that suggests treating SAD and PTSD with it. However, comparative effectiveness of cannabis to other pharmacological treatments for anxiety is yet to be determined. There is scope for further research on CTP use and mood disorders – both depression and bipolar disorders. Although CTP users widely report using CTP to improve mood and alleviate negative affect, the effectiveness of CTP in that regard remains obscure as does whether the relative benefits outweigh the risks of harm. The research into ADHD is in its infancy and more is needed. Comparative studies comparing the effects of CTP

to stimulant medications such as Ritalin and Adderall can provide insight in to the effectiveness of CTP. Longitudinal studies are required across the board to truly draw conclusions about CTP [65].

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