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REVIEW ARTICLE

Pros and Cons of Medical Cannabis use by People with Chronic Brain Disorders

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Abstract: ***Background*:** Cannabis is the most widely used illicit drug in the world and there is growing concern about the mental health effects of cannabis use. These concerns are at least partly due to the strong increase in recreational and medical cannabis use and the rise in tetrahydrocannabinol (THC) levels. Cannabis is widely used to self-medicate by older people and people with brain disorders such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), bipolar disorder, and schizophrenia.

***Objective*:** This review provides an overview of the perceived benefits and adverse mental health effects of cannabis use in people with ALS, MS, AD, PD, bipolar disorder, and schizophrenia.

***Results*:** The reviewed studies indicate that cannabis use diminishes some symptoms associated with these disorders. Cannabis use decreases pain and spasticity in people with MS, decreases tremor, rigidity, and pain in people with PD, and improves the quality of life of ALS patients by improving appetite, and decreasing pain and spasticity. Cannabis use is more common among people with schizophrenia than healthy controls. Cannabis use is a risk factor for schizophrenia which increases positive symptoms in schizophrenia patients and diminishes negative symptoms. Cannabis use worsens bipolar disorder and there is no evidence that bipolar patients derive any benefit from cannabis. In late stage Alzheimer's patients, cannabis products may improve food intake, sleep quality, and diminish agitation.

***Conclusion*:** Cannabis use diminishes some of the adverse effects of neurological and psychiatric disorders. However, chronic cannabis use may lead to cognitive impairments and dependence.

Keywords: Cannabis, dependence, cognition, neurological disorders, schizophrenia, bipolar disorder.

1. INTRODUCTION

Cannabis is one of the most widely used illicit drugs in the world. The United Nations Office on Drugs and Crime estimates that worldwide 3-5% of adults use cannabis [1]. The prevalence of cannabis use is very high in countries such as Ghana (21.5%), Zambia (17.7%), Canada (17.0%), the United States of America (US, 12.3%), and New Zealand (13.3%)[1]. It has been estimated that there are 20 million cannabis users in the US, including 1.2 million medical cannabis users [2, 3]. About 6 percent of Americans above the age of 18 will meet the DSM-5 criteria for cannabis use disorder at some point in their life [4].

In the US, federal law does not allow recreational or medical cannabis use. However, recreational and medical cannabis use is legal in an increasing number of states. Twenty-three states and the District of Columbia have legalized the medical use of cannabis and 4 states have legalized its recreational use. It is expected that cannabis use will continue to increase as there is growing tolerance towards the use of cannabis and an increase in the number of patients who use cannabis for medical purposes [5]. Most cannabis studies have investigated the effects of cannabis in healthy adolescents and young adults. However, cannabis is also used recreationally by older adults and by patients with neurological and psychiatric disorders to alleviate symptoms associated with their disorder. A large study with participants from 31 countries showed that 24.1% of cannabis users are between the ages of 51 and 60, 5.8% between 61 and 70, and 0.6% are older than 70 [6]. Cannabis use has more than quadrupled among the 55-59 year olds (1.6 to 7.4%) and doubled among 60-64 year olds (2.4 to 4.4%) between 2002 and 2012 [7].

In addition to the increase in cannabis use in the elderly, there has also been an increase in the use of cannabis for the

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treatment of neurological disorders [8, 9]. This is in combination with the dramatic increase in THC levels in cannabis which could lead to an increase in the number of people who experience adverse mental health effects [10]. In addition to cannabis, cannabis-based treatments such as nabiximols (trade name Sativex, cannabis plant extract, 1:1 ratio of CBD:THC), dronabinol (trade name Marinol, synthetic THC), and nabilone (trade name Cesamet, synthetic cannabinoid with chemical structure similar to THC) have also been used by people with brain disorders. Both nabilone and dronabinol have been approved by the US Food and Drug Administration (FDA) for the treatment of nausea and vomiting associated with chemotherapy for cancer and to stimulate appetite in AIDS patients with wasting syndrome. Nabiximols is already being used in 15 countries for the treatment of spasticity associated with multiple sclerosis (MS) and in the US, Sativex is being reviewed by the FDA for the treatment of cancer pain. The goal of this review is to provide insight into the potential beneficial and harmful effects of cannabis use and cannabis-based treatments in people with common neurological or psychiatric disorders and older individuals.

2. CANNABINOIDS

Cannabis has been used in religious ceremonies and for medical purposes for thousands of years [11]. Cannabidiol (CBD), the main non-psychoactive component of cannabis, was isolated in the 1940s and its structure was established in the 1960s [12, 13]. It wasn't until 1964 that tetrahydro-cannabinol (THC) was isolated [14]. Cannabidiol does not induce intoxication and diminishes the psychotropic effects of THC [15, 16]. The cannabinoids can be classified into three groups: phytocannabinoids, endocannabinoids, and synthetic cannabinoids [17]. More than one hundred phytocannabinoids have been isolated but in most commercial cannabis strains, only THC is produced in high levels [18]. Another phyto-cannabinoid that is sometimes expressed at high levels is CBD. Furthermore, two endocannabinoids have been discovered, namely 2-arachidonoyl glycerol (2-AG) and anandamide [19-21]. Some synthetic cannabinoids have a much higher potency than THC and have been associated with severe adverse mental health effects [22]. Cannabinoids mediate their effects *via* the activation of the cannabinoid type 1 (CB_1) and type 2 (CB_2) receptor. The endogenous ligands for these receptors are 2-AG and anandamide. The CB_1 receptor is one of the most common receptors in the central nervous system. High levels of CB_1 receptors have been detected in the hippocampus, basal ganglia, prefrontal cortex and cerebellum [23]. The localization of this receptor in the basal ganglia, hippocampus, and prefrontal cortex underscores the critical role of the cannabinoid system in the regulation of motor function and cognition [24]. The CB_2 receptors are mostly found in the periphery (thymus and spleen), but they have also been detected on cerebellar and brain stem neurons [25]. Cannabinoid type 2 receptor levels are extremely low in the healthy brain but their levels increase after injury and inflammation [26, 27]. The CB_2 receptors are mainly expressed on activated microglia, which play a critical role in the removal of dying cells but also induce the release of cytotoxic molecules that can lead to cell death [28, 29]. Activation of the CB_2 receptor decreases the release of cytokines and chemokines and diminishes inflammation and cell death [30, 31].

3. ANIMAL STUDIES

Studies with animals have provided evidence for the fact that chronic exposure to cannabis smoke, tetrahydrocannabinol (THC), or CB_1 receptor agonists leads to the development of dependence. Cannabis withdrawal leads to somatic withdrawal signs (*e.g.*, abdominal constriction, wet-dog shakes, head shakes, forepaw fluttering), anxiety-like behavior, and an increased release of the stress peptide corticotropin-releasing factor in the amygdala [32-35]. The negative affective state associated with drug withdrawal provides powerful motivation for the continuation of drug use [36, 37]. There is also extensive evidence that cannabis and THC impair memory and cognition in rodents. The eight-arm radial maze is a well validated test for investigating the neuronal mechanisms that underlie memory [38]. Nakamura *et al*. demonstrated that THC disrupts working memory in the radial maze test [39]. THC inhibits the release of acetylcholine in the hippocampus and this is likely one mechanism by which it impairs memory. This is supported by the observation that drugs that prevent the THC-induced decrease in acetylcholine release in the hippocampus also prevent memory impairments [40]. It has also been suggested that repeated THC administration leads to increased glutamate levels, which induces a downregulation of glutamate receptors and a reduction in the density of dendritic spines on hippocampal neurons. This may reduce synaptic plasticity and thereby cause memory impairments [41]. Memory impairments due to THC exposure may gradually diminish over time. In the above mentioned study by Nakamura *et al*., memory function returned to baseline levels after 4 weeks of abstinence [39]. Another study reported that memory function in mice was still impaired three weeks after the administration of one low dose of THC [42]. Therefore, this suggests that the memory function might recover after cannabis use, but only after an extended amount of time.

4. ACUTE EFFECTS OF CANNABIS USE

Cannabis has a wide range of subjective effects. The effects may vary between light and heavy users and can include feelings of intoxication, euphoria, altered sensory perception, cognitive and perceptual distortions, anxiety, dizziness, and increased appetite [43]. The most reliable markers of acute cannabis exposure are intoxication and tachycardia [44]. In terms of cognitive processes, there is extensive evidence that acute cannabis exposure impairs attentional tasks, consolidation and retrieval of memory, working memory, verbal memory, learning, and executive functions [44]. Impaired performance has been consistently found in multiple aspects of attention, including sustained attention, divided attention, selective, and focused attention [45]. Additionally, studies have found executive dysfunction related to cannabis exposure, including disinhibition and impaired decision making [46]. Acute cannabis intoxication in healthy young people causes slower reaction times, impaired accuracy, and impaired response inhibition [47, 48]. Other frontal dysfunction that has been observed

includes decreased information processing speed, poor planning, lack of self-monitoring, and inability to alter behaviors to suit changing tasks [49-51]. There can also be alterations in mathematical abilities and time perception, along with changes in the gross and fine motor skills [52, 53]. Taken together, these studies indicate that acute cannabis use affects emotional states and dramatically impairs cognitive processes and motor functions.

5. CHRONIC EFFECTS OF CANNABIS USE

One of the main adverse effects of cannabis use is the development of dependence. In the US, almost 10% of adults use cannabis and one third users meet the criteria for cannabis use disorder [54]. Cannabis use disorder is characterized by a strong desire to use cannabis, using larger amounts than intended, and continued usage despite negative social and physical consequences, craving, tolerance and withdrawal [55]. It has been estimated that 30% of regular cannabis users and 50-95% of heavy users experience a cannabis withdrawal syndrome [56]. Cannabis withdrawal is characterized by anxiety, depression, irritability, decreased sleep quality along with the quantity and stomach pain [57, 58]. This negative affective state plays a critical role in the maintenance of drug addiction [37]. Studies that have evaluated the long term effects of cannabis use on cognition are sparse. In one study in which participants were followed from birth to age 38, persistent cannabis users had a 6 point reduction in IQ compared to non-users [59]. Some longitudinal studies have shown persistent adverse effects of cannabis use on neurocognitive performance. These effects depend on the length of abstinence, age at the onset, or cumulative lifetime exposure [60]. Significant psychomotor dysfunction has also been reported in chronic cannabis users [61]. Some recovery of cognitive function might occur after cessation of cannabis use. Adolescent cannabis users with 3 weeks of sobriety demonstrated resolution of learning and verbal memory deficits, but continued to have difficulty with attentional tasks [62]. In one longitudinal study in young adults, episodic memory improved over an eight year abstinence period [63]. Taken together, this indicates that chronic cannabis use can lead to loss of control over cannabis use and cognitive impairments, which may diminish gradually after a prolonged abstinence period. Chronic cannabis use can also lead to what is called an amotivational syndrome [64, 65]. This amotivational syndrome is characterized by apathy, lack of motivation, and poor educational performance. Animal studies suggest that the amotivational syndrome is due to a THC-induced dysregulation of dopaminergic systems [66]. This is supported by a study with human cannabis users that showed that cannabis users with the highest level of apathy had the lowest dopamine synthesis capacity in the striatum [67].

6. STRUCTURAL CHANGES IN CANNABIS USE

There is extensive evidence for structural and functional abnormalities in young cannabis users. Chronic cannabis use leads to changes in gray (cell bodies, dendrites, and synapses) and white matter (myelinated neuronal tracts) architecture [68, 69]. There is some evidence that cannabis use may increase the volume of subregions of the cerebellum and amygdala in adolescents [70, 71]. The changes in the volume of these brain sites were associated with poor executive functioning (cerebellum) and internalizing problems (amygdala) [70, 71]. An increase in the volume of a brain site might be due to disrupted pruning of gray matter during a critical period in adolescence or possibly abnormal connectivity patterns that develop to compensate for cognitive deficits [72]. Although some studies reported that cannabis use can increase the size of brain regions, the great majority of the studies found that cannabis use decreases the volume of brain regions. Cannabis use-induced decreases in brain volume have been reported for the orbitofrontal cortex, hippocampus, striatum, and amygdala [69, 73-76]. One of the most consistent findings has been that cannabis use decreases the volume of the hippocampus and this correlates with the amount of cannabis used and the level of dependence [77]. It should be noted that a recent study reported that daily cannabis use does not affect the volume of the nucleus accumbens, amygdala, hippocampus, or cerebellum [78]. It was suggested that there was no effect of cannabis use on brain volumes because the study closely controlled for other factors that may affect the volume of specific brain sites, such as alcohol use. Taken together, conflicting findings about the effect of cannabis use on the volume of brain sites have been reported. Some of these differences might be due to difference in study design, comorbid drug use, and data analysis. Well controlled animal studies with young and old animals are urgently needed to evaluate the effects of cannabis smoke exposure on the volume of specific brain regions.

Cannabis use is most common among adolescents and young adults and this period is also critical for brain myelination. Cannabinoid receptors are found on myelinating glial cells and are thought to play a role in white matter integrity and connectivity [79]. A number of studies that investigated neuronal tracts in the brain using diffusor tensor imaging have found reductions in white matter integrity throughout the frontal and temporal lobes in adolescent cannabis users [68, 80-82]. These abnormalities are associated with psychological symptoms and cognitive impairments. Chronic cannabis use also leads to impairments in cerebro-vascular functioning, which has been associated with an increased risk for stroke [83, 84]. There is a lack of data regarding the effects of cannabis use on the brain of the elderly. The vast majority of cannabis studies have been conducted with young adults. Given the rapid increase in the aging population, it is critical to gain a better understanding of the acute and long-term effects of cannabis use in this group.

7. CANNABIS AND AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that rapidly progresses and primarily affects the motor neurons in the spinal cord and brain stem. One of the first symptoms is muscle weakness in one part of the body, which then spreads to other parts. Furthermore, thirty to fifty percent of ALS patients have signs of cognitive impairments [85, 86]. Amyotrophic lateral sclerosis is very rare in people before the age of 40, and the median age at diagnosis is 65 for males and 67 for females

[87]. The precise cause of ALS is unknown. However, several possible causes for ALS have been identified: 1) oxidative damage, 2) blockade of axonal transport by neurofilaments, 3) toxicity from intracellular aggregates, and 4) glutamate-mediated excitotoxicity [88]. Although it is not known what causes ALS, there is strong evidence that inflammation plays a role in its progression [89]. Amyotrophic lateral sclerosis has been associated with changes in the endogenous cannabinoid system and cannabinoid receptor agonists may slow down the progression of ALS by decreasing inflammation. Animal studies have shown that endogenous cannabinoid levels are elevated in spinal cord of symptomatic ALS mice [90]. Interestingly, CB_2 receptors, but not CB_1 receptors, are upregulated in a mouse model for ALS (G93A-SOD1 mutant mice) [91]. This observation is in line with a recent study in which CB_1 and CB_2 receptor levels were assessed in TAR-DNA binding protein-43 (TDP-43) mice [92]. These mice are considered an animal model for ALS [93]. TDP-43 aggregates have been detected in the brains of ALS patients and it has been suggested that these aggregates induce toxicity and cell death [94, 95]. Interestingly, in both male and female TDP-43 mice there is an upregulation of CB_2, but not CB_1, receptors in the spinal cord [92]. Treatment with THC, the synthetic CB_1 and CB_2 receptor agonist WIN55,212-2, and the selective CB_2 agonist AM-1241 delays ALS progression in animal models [91, 96]. Furthermore, the neuroprotective effects of THC are diminished by CB_1 receptor blockade [97]. Taken together, this suggests that both CB_1 and CB_2 agonists may slow down the progression of ALS.

Cannabinoids target multiple neuronal pathways and exert anti-inflammatory and neuroprotective effects. A post-mortem study showed that ALS patients have elevated CB_2 receptor levels on microglia in the spinal cord [98]. Unfortunately, CB_1 receptor levels were not assessed in the aforementioned study, but studies with animal models for ALS suggest that ALS is not associated with an upregulation of CB_1 receptors [91, 92]. Microglia do not express CB_2 receptors under baseline conditions but neuronal damage leads to microglia activation and the expression of CB_2 receptors [99].

Clinical studies suggest that cannabis may improve ALS symptoms. There is evidence that cannabis helps with pain, spasticity, drooling, appetite loss, and sleep [100, 101]. In patients with respiratory failure due to ALS, cannabis may help by inducing bronchodilation [102, 103]. Overall, these studies suggest that cannabis diminishes ALS symptoms and thereby improve the quality of life of patients. Clinical studies indicate that ALS is associated with high levels of anxiety and depression [104-106]. Small amounts of cannabis may help people to relax, induces euphoria, and decreases anxiety and thereby could also increase the quality of life of ALS patients [107-109]. Overall, the reviewed studies suggest that cannabis use may diminish some of the symptoms associated with ALS and delay disease progression (See Table **1** for an overview).

8. CANNABIS AND MULTIPLE SCLEROSIS

Multiple Sclerosis is a chronic demyelinating disease of the central and peripheral nervous system [110, 111]. The symptoms (*e.g.*, vision problems, muscle weakness, pain, balance problems, and paralysis) are due to uncontrolled or inappropriate neural transmission that gradually worsens when the disease progresses. During the early stage of the disease, patients may experience long periods during which they are relatively symptom free and these periods are interrupted by flare ups that lasts days to weeks. It has been suggested that cannabis, THC, nabiximols, and oral cannabis extract (OCE) may diminish spasticity associated with MS [112]. Thus far, one cannabis based drug (nabiximols) has been developed for the treatment of MS. Nabiximols is a mucosal spray that contains THC and CBD in a 1:1 ratio. The US FDA has approved nabiximols for clinical trials and it has been approved in several European countries, Canada, and New Zealand for the treatment of spasticity associated with MS.

Animal studies show that cannabinoid receptor agonists diminish tremors and spasticity in mouse models for MS [113]. Preclinical studies suggest that spasticity associated with MS is diminished by CB_1, but not CB_2, receptor agonists [114]. Cannabinoids have neuroprotective effects due to their action on microglial cells [115, 116]. Medical cannabis has been shown to decrease spasticity and pain in MS patients but it has negative effects on posture and balance [117, 118]. Furthermore, both nabiximols and THC decrease spasticity in MS patients [119, 120]. Oral cannabis extract has proven to be very effective for the treatment of central pain [119]. In addition to this, people with MS often suffer from severe bladder dysfunction due to the disruption of neuronal transmission between the brain and bladder. Some evidence suggests that nabiximols, but not dronabinol or oral cannabis extract, improves bladder function in people with MS [119, 121]. The cannabis based treatments did not reduce tremors in patients with MS [119, 122].

Multiple sclerosis has been associated with cognitive impairments, depression, and anxiety [123, 124]. It has been estimated that about 50% of MS patients have cognitive deficits and suffer from depression [125-127]. Multiple Sclerosis patients who smoke cannabis have more severe cognitive impairments than nonusers [128, 129]. Patients with MS who smoke cannabis perform poorly on tests for information processing speed, working memory, executive functioning, and visuospatial perception compared to ALS patients who do not smoke cannabis [129]. Multiple sclerosis patients who used cannabis were also twice as likely to be considered cognitively impaired [129]. Furthermore, in MS patients who use cannabis there is a correlation between cognitive impairments and reductions in gray and white matter volume in medial and lateral temporal regions, thalamus, basal ganglia, and prefrontal regions [130]. So far there is no evidence that cannabis use affects anxiety and depression in MS patients. Overall, the reviewed studies indicate that cannabis use may diminish spasticity and pain associated with MS, but chronic cannabis use has a detrimental effect on cognition in MS patients.

9. CANNABIS AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative brain disorder that decreases quality of life as it leads to bradykinesia (slow movements), rigidity, and tremors. Parkinson's has also been associated with non-motor symptoms that may

Table 1. Cannabis based treatments and expression of disease symptoms.

Disorder / Drug	Effect on Symptoms	Type of Study	Refs.
ALS			
Cannabis (smoked)	Appetite (↑), anxiety and depression (↓), Pain (↓), spasticity (↓), muscle relaxation (↑), drooling (↓), sleep (↑).	Survey	[101, 222]
THC (synthetic, dronabinol, drops)	Cramp intensity (=)	Clinical study	[223]
MS			
Cannabis (smoked)	Spasticity (↓), Pain (↓)	Clinical study	[117]
THC/CBD (nabiximols, oral spray)	Spasticity (↓), Pain (↓)	Clinical studies	[120, 224, 225, 226, 227]
THC (plant extract, oral capsule)	Muscle stiffness (↓)	Clinical study	[228]
THC (synthetic, dronabinol, capsule)	Spasticity (↓), Pain (↓)	Clinical study	[119]
THC (synthetic, nabilone, oral capsule, adjunct to gabapentin)	Pain (↓)	Clinical study	[229]
Parkinson's disease			
Cannabis extract (oral capsules)	Levodopa-induced dyskinesia (=), Parkinson's motor symptoms (=).	Clinical study	[142]
Cannabis leaves (oral leaves)	Rigidity (↓), bradykinesia (↓), resting tremor (↓), levodopa-induced dyskinesia (↓)	Survey	[138]
Cannabidiol	Quality of life (↑)	Clinical study	[230]
THC (synthetic, nabilone, oral capsule)	levodopa-induced dyskinesia	Clinical study	[141]
Alzheimer's disease			
THC (dronabinol, synthetic THC, oral capsule)	Agitation (↓), food intake (↑), sleep duration (↑)	Clinical study	[154]
THC (dronabinol, synthetic THC, oral capsule)	Disturbed behavior (↓), body weight gain (↑)	Clinical study	[155]
THC (dronabinol, synthetic THC, oral capsule)	Nocturnal motor activity (↓), agitation (↓), appetite disturbances (↓), irritability (↓)	Clinical study	[156]
THC (nabilone, synthetic)	Agitation (↓), resistance during care (↓)	Case report	[231]
Schizophrenia			
Cannabidiol	All schizophrenia symptoms (Brief Psychiatric Rating Scale) (↓)	Case report	[232]
Cannabidiol	Positive and negative symptoms (↓)	Clinical study	[185]
Bipolar disorder	Not evaluated in clinical studies		

include psychosis, cognitive impairments, anxiety, and depression [131]. Parkinson's symptoms are at least partly due to the loss of dopaminergic neurons in the substantia nigra, which leads to a dysregulation of the extrapyramidal system. There is evidence that the endocannabinoid system is dysregulated in PD patients. It should be noted, however, that at this point it is not known if a dysregulation of the endocannabinoid system contributed to the development of PD or that PD leads to changes in the endocannabinoid system. Patients with PD have elevated levels of anandamide in the cerebrospinal fluid (CSF) and decreased CB_1 receptor levels in the basal ganglia [132, 133]. Animal studies suggest that drugs that target the cannabinoid system might diminish PD's motor symptoms and slow disease progression. In a Marmoset PD model, THC improved both activity and hand-eye coordination [134]. The phytocannabinoid Δ9-tetra-hydrocannabivarin (THCV; CB_1 receptor antagonist and CB_2 receptor agonist) attenuates motor inhibition in the 6-hydro-xydopamine (6-OHDA) model of PD [135]. Furthermore, the cannabinoids THC and CBD diminish the neurotoxic effects of 6-OHDA, and these effects might be mediated by their antioxidant or anti-inflammatory properties [136]. In the same animal model, a drug treatment (AM404) that enhanced anandamide levels also decreased PD symptoms [137]. Therefore, there is strong preclinical evidence that increasing cannabinoid tone diminishes PD symptoms.

Clinical studies suggest that cannabis may diminish the motor symptoms associated with PD [138, 139]. A small study with 22 patients showed that smoking cannabis improves motor symptoms such as resting tremor, rigidity, bradykinesia, and posture. In the same study, cannabis also decreased pain and improved sleep quality [139]. It has also been reported that CBD diminishes REM sleep behavior disorder in people with PD [140]. Furthermore, the synthetic cannabinoid receptor agonist nabilone attenuates levodopa-induced dyskinesia in PD patients [141]. Oral cannabis extract or CB_1 receptor blockade with rimonabant does not improve motor symptoms associated with PD [142, 143]. Overall, clinical studies suggest that cannabis, CBD, and synthetic cannabinoid agonists may diminish motor symptoms and pain associated with PD. At this point, only a few relatively small studies have been conducted and additional studies are needed before firm conclusions can be drawn about the effect of cannabis on PD. Furthermore, before medical cannabis can be recommended to PD patients, clinical studies are needed to investigate the effects of cannabis on non-motor systems (hallucinations, cognitive impairments) associated with PD.

10. CANNABIS AND ALZHEIMER'S DISEASE

Neurocognitive disorders are increasingly prevalent in the aging population. Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder. Alzheimer's is truly a brain disease of the elderly; 4.3% of the 75-80 year olds and 28.5% of the 90 year olds has been diagnosed with AD [144]. The majority of AD patients are between the ages of 80 and 85. One of the first clinical symptoms is memory impairment and this is followed by language and behavioral problems. Alzheimer's is characterized by the loss of synapses and lesions that include plaques composed of an amyloid (Aβ) core and neurofibrillary tangles that mainly consist of hyperphosphorylated tau [145]. Alzheimer's has significant effects on the expression of CB_2 receptors in the human brain. One study reported a high level of CB_2 receptor expression in microglia associated with β-amyloid-enriched neuritic plaques while CB_2 receptors were not detected beyond the borders of the plaques or in the brains of healthy controls [146]. In contrast, AD does not lead to changes in CB_1 receptor levels [146, 147]. The therapeutic effects of the cannabinoids are hypothesized to be due to their antioxidant, anti-inflammatory, and neuroprotective effects, which may diminish the effects of beta-amyloid toxicity [148, 149]. Animal studies indicate that compounds that elevate endocannabinoid levels decrease the toxic effects of beta-amyloid peptide [150]. Furthermore, studies with an AD mouse model (amyloid-protein precursor/presenilin 1) show that a THC-CBD mixture decreases amyloid beta levels and reverses learning impairments [151]. In the same animal model, a CB_2 receptor agonist improves cognition, decreases tau hyper-phosphorylation, and decreases the expression of pro-inflammatory cytokines [152]. Therefore, cannabinoid based treatments could potentially slow the progression of AD.

Cannabis might also be effective for the treatment of late stage AD symptoms [153]. Several studies have investigated the effects of dronabinol, which is a synthetic version of THC, in late stage AD patients. These studies showed that dronabinol improves food intake, sleep duration, circadian rhythm, and decreases agitation in late stage AD patients [154-157]. The patients received dronabinol for only a short period of time and it was not investigated if dronabinol affects memory and cognition. Therefore, additional studies are needed to investigate the long-term cognitive effects of THC or THC-like compounds in AD. Overall, these studies suggest that cannabis may slow down the progression of AD and decreases some its symptoms. However, additional insight into the effects of cannabis on cognition in AD patients is needed.

11. CANNABIS AND BIPOLAR DISORDER

Bipolar disorder is characterized by major depressive and manic episodes or episodes with mixed depressive and manic symptoms [55]. Cannabis is the most often used illicit drug in patients with bipolar disorder and people with bipolar are seven times more likely to use cannabis than controls [158, 159]. It was initially believed that cannabis might have some therapeutic effects in bipolar patients, but this is not supported by recent findings [160]. Cannabis use is associated with an early age of onset of bipolar disorder, increased severity, and increased disability [161-163]. Cannabis use in patients with bipolar also further increases the risk for suicide [159]. A prospective study showed that cannabis use is associated with a decrease in long-term remission for bipolar disorder [164]. A large epidemiological study indicated that cannabis use increases the risk for manic symptoms [165]. Cannabis also worsens global functioning in patients with bipolar disorder [166]. There is no indication for CB_1 receptor level changes in people with bipolar disorder [167]. However, a single nucleotide polymorphisms in the CB_2 receptor gene (SNP, rs41311993, 524C>A; Leu133Ile) is more common in people with bipolar disorder than in healthy controls [168]. This gene has been associated with CB_2 receptor stability and therefore changes in the CB_2 receptor could possibly contribute to the development of bipolar disorder. Finally, cannabis may alter the metabolism of medications prescribed for bipolar disorder. Overall, there are no clear indications that bipolar patients derive a benefit from cannabis use.

12. CANNABIS AND SCHIZOPHRENIA

Schizophrenia is a mental disorder that typically presents in late adolescence or early adulthood and is among the top ten leading causes of disability in the world [169]. Schizophrenia is characterized by three core symptom groups: positive symptoms (hallucinations, delusions, grandiosity, paranoia, and suspiciousness), negative symptoms (blunted affect, social avoidance, poor rapport, lack of motivation, lack of spontaneity, and emotional withdrawal), and cognitive dysfunction [170]. Cannabis use is more common among people with schizophrenia than in the general population [171]. In Western countries, 10%20% of the general population use cannabis while 30%50% of people with schizophrenia use cannabis [172, 173]. There are several possible explanations for this. Cannabis might be more rewarding in people with schizophrenia, it might compensate for brain deficits, or people with schizophrenia have less control over drug use.

There is extensive evidence that the endogenous cannabinoid system is dysregulated in people with schizophrenia. Anandamide levels are elevated in the CSF of schizophrenia patients [174]. Furthermore, post mortem studies have shown an increase in CB_1 receptor levels in schizophrenia patients, especially in the dorsolateral prefrontal cortex, pons, cingulate cortex, and nucleus accumbens [175-180].

There is extensive evidence that cannabis use increases the risk for schizophrenia [181]. A large study with 50,087 Swedish men showed that cannabis users are 7 times more likely to develop schizophrenia than people who do not use cannabis [182]. This is in line with another large study that reported an increase in cannabis use in people in the year before they were first diagnosed with schizophrenia [183]. It should be noted that the harmful effects of cannabis depend on the THC:CBD ratio [181]. THC increases the risk for psychosis but CBD diminishes the effects of THC and even has antipsychotic effects in people with schizophrenia [184, 185]. During the last decades there has been an increase in THC levels in cannabis and CBD levels have remained the same. From 1980 to 2008, the THC concentration in cannabis products increased from 3 to 9 % while CBD levels remained stable at 0.4 % [186]. This suggests that cannabis use is more likely to lead to psychiatric illness and in particular in people who are genetically predisposed to develop schizophrenia [187, 188].

It is interesting to note that electroencephalography (EEG) studies have revealed that chronic cannabis use disrupts the brains ability to generate synchronized neuronal oscillations (beta and gamma band activity) [189, 190]. Neuronal oscillations play a critical role in coordinating the activity between brain sites and a disruption in synchronized neuronal activity can affect a wide range of brain functions. Chronic cannabis use induces similar disruptions in neuronal synchronization as those observed in people with schizophrenia [191]. Therefore it has been suggested that cannabis' effect on neuronal oscillations may contribute to the development of schizophrenia (for an extensive review on this topic see [191, 192]).

Cannabis use has a detrimental effect on some schizophrenia symptoms. Cannabis use worsens positive symptoms (mainly hallucinations), leads to poor treatment outcomes, and increases the risk for relapse after a period of remission [193-196]. It has been suggested that cannabis use disrupts the endogenous cannabinoid system in the prefrontal cortex and thereby induces changes in glutamate and GABA release, which contributes to the development of schizophrenia [197]. The effects of cannabis use on dopaminergic systems might also play a role in the development of schizophrenia. The catechol-O-methyltransferase (COMT) gene plays an important role in the breakdown of dopamine, and a valine to methionine mutation ($Val^{158}Met$) in this gene leads to a decrease in dopamine metabolism [198]. It has been suggested that this mutation by itself does not increase the risk for schizophrenia but increases the risk for schizophrenia in people who use cannabis [199]. There is some evidence that cannabis use may diminish the negative symptoms of schizophrenia. Several small studies suggest that a majority of people with schizophrenia use cannabis to diminish negative symptoms [200, 201].

The adverse effects of cannabis use might be more severe for people with schizophrenia than for healthy controls [202]. Cannabis use leads to a larger decrease in gray matter volume in people with schizophrenia than in healthy controls [202]. Interestingly, the decrease in gray matter volume was greatest in brain areas with high levels of CB_1 receptors such as the dorsolateral prefrontal cortex and the anterior cingulate cortex [203]. Despite the negative effect of cannabis use on gray matter volume in people with schizophrenia, several studies suggest that people with schizophrenia who use cannabis have better cognitive function than people with schizophrenia who do not use cannabis [204-208]. However, it has also been reported that people with schizophrenia who use cannabis have worse cognitive function than patients who do not use cannabis [209]. It should be noted that it might be possible that cannabis use does not improve cognition but that patients who use cannabis have less severe cognitive impairments than non-cannabis users. It has been hypothesized that cannabis use in vulnerable young people can lead to a type of schizophrenia that is characterized by psychosis and only mild cognitive impairments [208, 210]. In contrast, people who do not use cannabis and develop schizophrenia have psychotic symptoms and also severe cognitive impairments.

The endogenous cannabinoid system has been identified as a target for the treatment of schizophrenia [169]. Since the 1970's it has been suggested that the cannabinoid CBD has antipsychotic properties [211]. In the prepulse inhibition (PPI) paradigm in healthy humans, a weak pre-pulse inhibits the strong startle response caused by an intense stimulus (*e.g.*, loud noise) [212]. However, this inhibitory response is disrupted in people with schizophrenia (*i.e.*, impaired PPI) [213]. Drugs that induce schizophrenia-like symptoms in humans such as the NMDA receptor antagonists MK-801 and ketamine also disrupt PPI in rats [212]. A wide range of antipsychotic drugs diminish the PPI impairment induced by NMDA receptor antagonists [214]. Interestingly, recent studies suggest that CBD also attenuates the PPI impairment induced by the NMDA receptor antagonist MK-801 or amphetamine [215-217]. This suggests that cannabis might mediate some effects that resemble those of antipsychotic drugs.

Taken together, cannabis has a complex effect on schizophrenia and the effect might depend on the THC and CBD levels in cannabis. Regular use of cannabis with high levels of THC has detrimental effects on gray matter and positive symptoms of schizophrenia. On the other hand, cannabis does not seem to worsen the cognitive symptoms associated with schizophrenia and might diminish some of the negative symptoms. Cannabis with high levels of CBD and low levels of THC could possibly prevent some of the deficits in sensory motor gating in patients with schizophrenia.

CONCLUDING REMARKS

The goal of this article is to provide an overview of the benefits and negative mental health effects of cannabis use by people with a neurological disorder, bipolar disorder, or schizophrenia. The reviewed studies indicate that cannabis use has complex effects and its effects depend on the specific brain disorder for which it is being used. Clinical studies

provide evidence that cannabis might diminish some of the symptoms associated with PD, ALS, and MS. Cannabis use may decrease spasticity and pain in people with MS, decrease tremor, rigidity, and pain in people with PD and improve the quality of life of ALS patients by improving speech and swallowing, and decreasing spasticity. There is also evidence that people with schizophrenia use cannabis to diminish some of the symptoms of their disorders. Cannabis use might temporarily improve the negative symptoms of schizophrenia. There is currently no evidence that people with bipolar disorder derive any benefit from cannabis. The acute and chronic effects of cannabis use in the elderly are poorly understood. Aging is associated with physiological and neurological changes that may affect the response to cannabis. Changes in lean and fat mass may affect the volume of distribution of THC, and impairments in THC clearance may lead to elevated drug levels and increased drug interactions [218, 219]. Cannabis has large effects on neurotransmitter release in the hippocampus and prefrontal cortex and these brain sites also undergo changes during aging [220, 221]. Because cannabis use in the elderly is on the rise, clinical and preclinical studies are urgently needed to investigate the physiological and neurological effects of cannabis use in the elderly.

Taken together, many people with PD, ALS, MS, and schizophrenia smoke cannabis to diminish the symptoms associated with their disorder. It should be noted that while short term use of cannabis could diminish some of the symptoms of these disorders, chronic cannabis use can have adverse long-term effects. It has been firmly established that chronic cannabis use can lead to the development of dependence, cognitive impairments, which increases the risk for depression and anxiety. Cannabis also has adverse physiological effects such as increasing the risk for lung diseases and has negative effects on male and female reproductive systems. Overall, acute cannabis use might provide temporary relief from a wide range of symptoms associated with neurological and psychiatric disorders, but prolonged heavy cannabis use might have adverse effects on mental and physiological health.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest. One of the authors (AB) was supported in part by an NIH grant (DA039349) when working on this review.

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