Cannabis and Brain: Disrupting Neural Circuits of Memory

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Abstract: Cannabis is a federally controlled substance, it's very familiar to many but its neurobiological substrates are not well-characterized. In the brain, most areas prevalently having cannabinoid receptors have been associated with behavioral control and cognitive effects due to cannabinoids. Study over the last several decades suggested cannabinoids (CBs) exert copious oftentimes opposite effects on countless neuronal receptors and processes. In fact, owing to this plethora of effects, it's still cryptic how CBs trigger neuronal circuits. Cannabis use has been revealed to cause cognitive deficits from basic motor coordination to more complex executive functions, for example, the aptitude to plan, organize, make choices, solve glitches, remember, and control emotions as well as behavior. Numerous factors like age of onset and duration of cannabis use regulate the severity of the difficulties. People with the cannabis-linked deficiency in executive functions have been found to have trouble learning and applying the skills requisite for fruitful recovery, setting them at amplified risk for deterioration to cannabis use. Exploring the impacts of cannabis on the brain is imperative. Therefore the intention of this study was to analyze the neuropsychological effects and the impact of CBs on the dynamics of neural circuits, and its potential as the drug of addiction.

Keywords: Cannabis, Cannabinoids, Marijuana, Brain, Neural Circuits, Memory.

INTRODUCTION

Cannabis, also known as marijuana, is a drug usually obtained from the cannabis plant used for medical as well as recreationally [1]. Tetrahydrocannabinol (THC), one of 483 known CBs is the major active compound in cannabis and is one of the known compounds in the plant [2], together with a minimum of 65 other CBs [3]. Cannabis extract or preparation by smoking, vaporizing and within food can be used [4]. Although it is mostly used for recreational and medicinal purposes, it might be employed in religious and other spiritual cases. In 2013, about 128 million to 232 million of the population have used cannabis (i.e. comprising of 2.7-4.9% world's population between 15 and 65) [5]. Similarly, by 2015, the use of cannabis by Americans increased from 43% to almost 51 percent in 2016 [6]. These cannabis statistics made it most common amongst illegally used drugs in the United and consequently the world in general [4,7].

Medical cannabis is used to refer cannabis usage to treat manage, disease treatment or improve symptoms; although, a single accurate definition might still not be agreed-upon [8]. There has been no rigorous scientific study on the medical usage of cannabis so far, mostly as a result of restrictions and government laws attached to the production [9]. Evidence suggesting the use of cannabis in chemotherapy to facilitate nausea reduction and profuse vomiting, improving the appetite of patients suffering from acquired immune deficiency syndrome (AIDS) and treatment of other muscular pains and convulsive movements muscle spasms, have been limited [10-12]. The use of cannabis for other medicinal cases is not sufficient for confirm about its harmless effects and efficacy. Increase in both major and minor adverse effects is associated with major and minor short-term usage [11]. Dizziness, feeling tired, vomiting, and hallucinations are common side effects [11]. Effects of the continuous use of cannabis for longer periods have not been clear [11]. While addiction risks, schizophrenia, accidental intake by children, memory and other behavioral problems are the major concerns here [10].

The physical as well as cognitive effects associated with cannabis intake including the feeling of high or

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stoned, a general alternation of feelings, euphoria, and a rise in appetite change [13]. When smoked, feelings of such effects begin to appear in the first thirty minutes to an hour minutes after being cooked and eaten [13,14]. The strength and period of these feelings continuous of about last for up to six hours. Consequently, the decrease in temporary memory storage, dry mouth, disturbed motor responses, paranoia, coloration of the eyes are mostly the temporary and short side effects [13,15]. However, disturbed cognitive abilities, desired feelings, particularly with individuals starting during teenage ages and cognitive disorders with children having cannabis using mothers during periods of pregnancy have regarded as some of the long-term effects [13]. Psychosis, characterized by impaired reality relationships, has been strongly related to the use of cannabis [16], although arguably related [17].

Most countries of the world have banned the possession, use, and sale of cannabis and declared them illegal [18,19]. The consequences of heavy and long-term exposure may be related with liver diseases especially in individuals with increased risk of hepatitis C, cardiovascular diseases as well as breathing and lungs' diseases, heart, and vasculature, in addition to social effects, relationship, biological, behavioral and physical effects [20]. During as well as before pregnancy, cannabis use is recommended be stopped as it can result in defects to the baby and affect the health of the mother [21,22]. However, low birth weight or early delivery has been shown to be not associated with maternal use of marijuana during pregnancy upon tobacco control and other contributing factors [23]. In 2014, a study showed that although the use of cannabis might have significantly lower harmful effects compared to alcoholism, thus it could only be premature to substitute it with problematic drinking without much evidence from further studies [24]. Similarly, some other effects may include cannabinoid hyperemesis syndrome [25,26]. Cannabis-based medications have been a theme of intense study owing to amplified uses and copious health hazard effects as well as the discovery of the endogenous cannabinoid system. Therefore the purpose of this study was to analyze the effect of CBs on brain including disrupt memory encoding and demonstrate its addictive potentiality.

MECHANISM OF ACTION OF CANNABINOIDS

In the central nervous system, the brain and the spinal cord are cannabis main sites of action. It binds the two G-protein-coupled receptors, CB1 and CB2. CB1 receptors are highly expressed in the brain and are located in many regions of the cerebellum, ganglia, spinal cord, peripheral nerves and hippocampus (Figure **1**) [27-29]. Mechanism of action of cannabis involves its antagonistic effects on CBI receptor thereby inducing and facilitating behavioral and mental disturbance. Cannabis changes individuals' perceptions and behavior, disrupting memory and storage, affects learning and judgment via its action on the CB1 receptor (Table **1**). Additionally, cannabis also

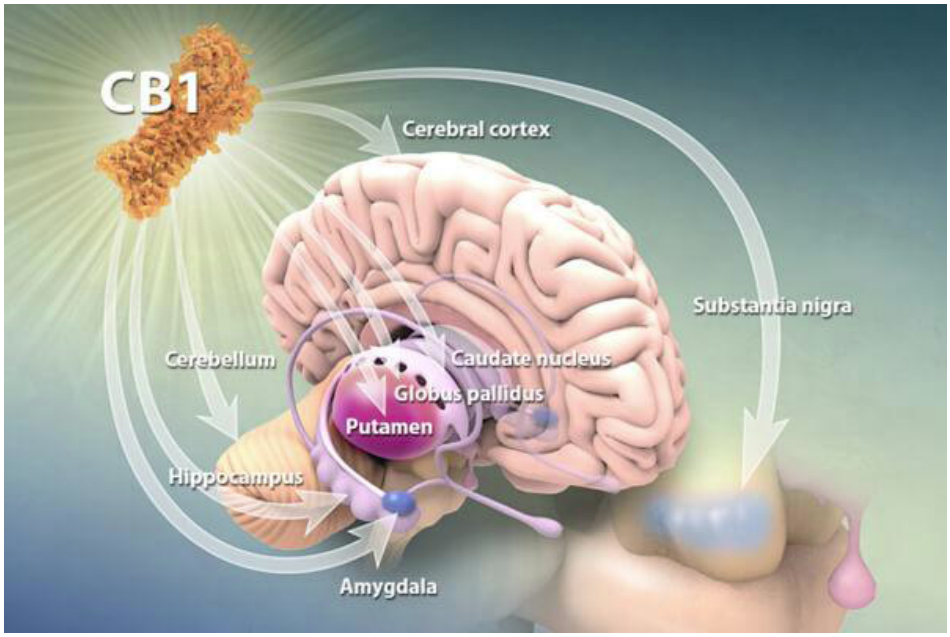

Figure 1: The effects of cannabis on the different parts of the brain (Adapted from [28]).

Table 1: The Behavioral Effects of THC on the Brain [32]

Brain Structure	Regulates	THC Effect on User
Amygdala	Emotion, fear, anxiety	Panic/paranoia
Basal ganglia	Planning a movement	Slowed reaction time
Brainstem	Information amid brain and spinal column	Antinausea effects
Cerebellum	Motor coordination, balance	Impaired coordination
Hippocampus	Learning new info	Impaired memory
Hypothalamus	Eating, sexual behavior	Increased appetite
Neocortex	Complex thinking, feeling and movements	Altered thinking, judgments and sensation
Nucleus accumbens	Motivation and rewards	Euphoria
Spinal cord	Transmission of info amid body and brain	Altered brain sensitivity

disrupts coordinated response, behavior and could promote psychosis and incoordination of time and proper body movement [27,30]. As such, cannabis was originally classified as a hallucinogen due to these perceptual aberrations. Cannabis causes addiction and most other behavioral abnormalities by over-activating the endocannabinoid system, also known as the cannabinoid system of the body [29,30].

Antagonism of 5-HT3 receptors by cannabis mediates the anti-emetic effects [31]. In contrast, peripheral tissues particularly the spleen, immune cells and the blood system are the location of the CB2 receptors in the body. The immunosuppressive activity of cannabis maybe due to these receptors [29]. These G-protein coupled cannabinoid receptors (i.e. CB1 and CB2) inhibit the enzyme adenylate-cyclase resulting in their activation. This activation decreases levels of glutamate and acetylcholine, two important neurotransmitters that indirectly affects opioid, serotonin, γ-aminobutyric acid and N-methyl-D-aspartate, opioid and serotonin receptors. The location of these cannabinoid receptors being presynaptic rather than postsynaptic explains their modulation of the neurotransmitter releases [30].

In a recent study, cannabis was shown to decrease dopamine responses in the brain's reward center, particularly at the mesolimbic region of the dopamine system. Through the dopamine neurons, the neurotransmitter dopamine is responsible for the effects of pleasure in the midbrain and the reward center. However, hippocampus, nucleus accumbens, prefrontal cortex and the amygdala are the major components of the limbic system. Thus in addition to effects of reward and pleasure, regulation and control of movement, compulsion and preservation are also associated with mesolimbic dopamine system as well.

NEUROLOGICAL EFFECTS OF CANNABINOIDS

Regions controlling body movement, learning, cognitive abilities and reward such as the hippocampus, basal ganglia and the accumbens all contain highly abundant cannabinoid receptors. While such regions controlling involuntary and fear responses, sensations, sleep, maintenance of internal environment and other peripheral responses contain only moderate amounts of cannabinoid receptors [33].

Experiments on human as well as other animal tissue have demonstrated a disruption of short-term memory formation [34] which is consistent with the abundance of CB1 receptors on the hippocampus, a region in the human brain associated with and regulating memory. Cannabinoids inhibit the release of several neurotransmitters including norepinephrine, acetylcholine and glutamate in the hippocampus thereby decreasing activity of neurons in the region. The activity decrease represents similar signs with a temporary hippocampal lesion [34].

Higher concentrations of THC used in an *in vitro* experiment showed a competitive inhibition of the enzyme AChE with its substrate and amyloid β (Aβ) peptide aggregates inhibition, seen in development of Alzheimer's' disease (AD). Although THC might have superior inhibition capabilities on Aβ aggregation compared to recent drugs approved for AD treatment thus indicating an unexploited mechanism by which cannabinoid could be used to affect development of the [35].

PSYCHOLOGICAL EFFECTS OF CANNABINOIDS

The principal effect of cannabis, the high feeling, is mostly subjected and depends upon method of

cannabis use and individuals. Upon its entry into the bloodstream, it travels to the brain and binds to cannabinoid receptors. The mechanism of action of N-arachidonoylethanolamine (i.e. anandamide), an endogenous ligand for the cannabinoid receptors is mimicked by THC [36]. This action causes the *in vivo* changes in the neurotransmitter levels such as epinephrine and dopamine whose actions are related to the resulting cannabis ingestion effects such as anxiety and euphoria [37]. Some other effects could include changes in perception, sensation, higher responses, decreased depression, stimulated effects and increased sexual activity/performance [38]. Additionally feeling of anxiety and paranoia, hallucinatory thinking is also typical effects of cannabis ingestion. Major side effects of marijuana ingestion are increased responses and feelings of anxiety. Although some group of cannabis smokers reported anxiety after longer periods, about 30 percent smokers reported immediate increased in sensual and anxiety effects [39]. Although lack of experience in cannabis use and an improper environment could be factors attributing to such anxiety feelings after smoking or ingestion. Cannabidiol (CBD) is also a cannabinoid usually found in different amounts and has been indicated to improve effects experienced by users such anxiety by THC [40].

Although mostly having adverse effects, beneficial effects of cannabis such as increased food aroma and test, improve mood, memory retention, music and sound appreciation, improve ideas and thought, innovation, deep thought and calm, have been reported. However higher doses of cannabis have adverse effects including hallucinations, heart and breathing problems, instability in vision and disproportionate behavior and responses. Cannabis can also cause loss of personality and disruption of normal state in some cases [41,42].

The accompanying effects of acute psychosis after cannabis mostly wanes after brief periods (i.e. up to 6 hours), although regular cannabis users could have effects persisting for days [43]. Physical restraint may also be necessary particularly in cases accompanied by sedative effects and aggression [43].

Cannabis comprises a mixture of stimulant, depressant and hallucinogen properties although some drugs with pyschoactivities could clearly be in either only one of such category, despite the dominant hallucinating effects, some other effects has been seen. Cannabis plant, though reported to be having variety of cannabinoids such as CBD with psychoactive effects, THC is the most active component of the plant according to various studies [44,45].

THERAPEUTIC EFFECTS OF CANNABIS

Natural forms of cannabis have been claimed to be used therapeutically in treatment of some diseases and conditions and this has been referred to as medical cannabis or marijuana [46]. Despite this however, the use of cannabis in either local or herbal forms is yet to be recognized around the world by various regulating agencies [47].

The Food and Drug Administration (FDA) has only approved the synthetic forms of cannabis rather than the natural forms of medicinal uses. Two different synthetic forms approved by FDA are on the market. Those are dronabinol (i.e. Marinol) and nabilone (i.e. Cesamet). These two synthetic forms are the FDA approved for the indications as an appetite enhancer in AIDS patients and for nausea in patients undergoing chemotherapy [47,48].

Numerous therapeutic effects are exerted by various cannabis preparations. They are effective against some psychiatric diseases as well as having pain-relieving and anti-inflammatory effects, neuroprotective and antiemetic actions [49]. However, only one cannabis extract is approved currently for use. In 2011, it was approved for treating acute and much less chronic contractile dysfunction in multiple sclerosis (MS). It was licensed in 2011 for treatment of moderate to severe refractory spasticity in MS and contains proportions of THC and CBD (Table **2**). While by June 2012, it was revealed by the German Joint Federal Committee that extracts of cannabis could be having additional benefits and this has led to temporary license for use up to 2015.

Nabiximols, an extract of cannabis has also been approved in Germany and other places as an effect sublingual spray. Although since 1985, dronabinol has already been licensed as an antiemetic agent as well as in AIDS for appetite loss in the USA. However, the use of nabilone to alleviate chemotherapy side effects in cancer patients in Great Britain has been sanctioned [49].

CANNABIS AND NEURAL CIRCUITS

Although there are less or no much scientific evidence, prolong use of cannabis could be a cause for permanent brain damage [51,52]. Thus it has been reported that ex-cannabis users have the deficiency in

Table 2: The Evidence for the Safety and Effectiveness of Medical Cannabis [50]

Condition	Form	Finding	Strength of Evidence
MS: Spasticity and related symptoms	Oral cannabis extract (OCE)	Can reduce patients' reported symptoms of spasticity	Strong
	OCE	Probably does not lead to improvement short-term (12-15 weeks) on tests for spasticity a doctor performs	Moderate
	Synthetic THC	Can probably reduce patients' reported symptoms of spasticity • Can probably lessen cramp-like pain or painful spasms • Probably does not lead to improvement short-term (15 weeks) on tests for spasticity a doctor performs	Moderate
	Oral spray (Nabiximols)	• Can probably lessen patients' reported symptoms of spasticity short-term (6 weeks) • Probably does not lead to improvement short-term (6 weeks) on tests for spasticity a doctor performs • Can probably lessen cramp-like pain or painful spasms	Moderate
	OCE and synthetic THC	• Might lessen patients' reported symptoms of spasticity if continued for at least one year • Might lead to improvement on tests for spasticity a doctor performs, if treatment continued for at least one year	Weak
	Smoked cannabis	• Not enough evidence to show if safe or helpful for pain related to spasticity	Unknown
MS: Central pain	OCE	• Can help lessen central pain (feelings of painful burning, "pins and needles," and numbness)	Strong
MS: Bladder problems	OCE and synthetic THC	• Probably do not help lessen frequent urination and bladder control problems Oral Spray (Nabiximols) • Probably helps lessen frequent urination (at 10 weeks)	Moderate
	Oral spray (Nabiximols)	• Not enough evidence to show if helps lessen bladder problems overall	Unknown
MS: Tremor	OCE and synthetic THC	• Probably do not help lessen tremor in MS	Moderate
	Oral spray (Nabiximols)	• Might not help lessen tremor in MS	Weak
Parkinson's disease: Temporary, uncontrolled movements	OCE	• Probably does not help lessen abnormal movements caused by levodopa	Moderate
Huntington's disease: Motor symptoms	Synthetic THC	• Not enough evidence to show if helps lessen motor symptoms	Unknown
Tourette Syndrome: Tic severity	Synthetic THC	• Not enough evidence to show if helps lessen tic severity	Unknown
Cervical Dystonia (i.e. abnormal neck movements)	Synthetic THC	• Not enough evidence to show if helps lessen abnormal neck movements	Unknown
Epilepsy: Seizure frequency	Any form of cannabis	• Not enough evidence to show if helps lessen how often seizures occur	Unknown

memory and information retraction abilities [53], but there was no clear evidence of impairment cognitive function [54]. Consequently, cannabis effects on work and performance or leading to amotivational syndrome [51,55], nor any confirming evidence that cannabis users might develop neuronal complications in the

brain [55] Recent studies on cannabis use using advanced techniques and modern neuroimaging methods have provided a backing to previous studies. For instance, in a study with 18 young adults frequently using cannabis, the magnetic resonance imaging test results when compared with 13 nonfrequent users showed the absence of alterations in brain tissue volumes or cerebral atrophy [56].

Rather, studies on other animal models were different. A decrease in neural density and damage to the hippocampal CA3 zone were seen in rats after oral administration of increased doses of THC for 3 months [57] or after 8 months of subcutaneous administration [58]. Surprisingly, in a study with a synthetic cannabinoid WIN55,2122, there was a more rapid development of the hippocampal region with increase neural and dendritic size and density after administration to rats twice daily (i.e. 2 mg/kg). However in an overall study with both rats and mice, no major tissue and muscular changes were seen although 50 mg/kg/day and 250 mg/kg/day of THC were administered for 5 days in rats and mice [59]. Similarly, a related study on larger rhesus monkeys exposure to smokes of cannabis showed less significant histopathological changes [60,61] despite certain septal and hippocampal changes in a small number of the monkeys [62].

Although, there were no consistent results after an *in vitro* studies on cannabinoids effects on neurons in the brain. The survival rate of rats' cortical neurons exposed to about 5 μM of THC for 2 hours had massively increased as compared with controls [63]. Concentrations of THC as low as 0.1 μM have effects on the neurons significantly. Consequently, THC effects have been associated with cytochrome c release leading caspase 3 activation and initiation of apoptosis. Certainly, inhibition through the CB1 receptors could lead to blocking of these effects particularly using pertussis toxin or the antagonist, AM251. In a similar study, defects due to death of the hippocampal neural cells after exposure to 1 μM drug of THC for 5 days which increased with almost 50% cell deaths with only 2 hours exposure to 10 μM THC, have been reported [64]. However in this case, the effects were only blocked by the antagonist, rimonabant not pertussis toxin. Simultaneously, mechanisms associated with formation of free radicals upon arachidonic acid release were proposed. However, there was no any observed damage when cortical neurons of rats exposed to 1 μM THC for about 15 days though other authors reported massive cell death in C6 glioma cells of rats, mouse N18TG12 neuroblastoma cells and even human U373MG astrocytoma cells when exposed to similar 1 μM of THC [65]. In a remarkable study, there was rather an increase cell survival after injection of THC to solid tumors of C6 glioma in rodent brain with seemingly 20-35% of the animals having no tumor [66]. This could rather spell a potential role of THC and other cannabinoids in cancer treatment [67].

Cannabinoids have also been reported to have neuroprotective roles. *In vivo* studies on rat showed decrease damage in hippocampus upon WIN55,2122 administration in focal ischemiamodels [68]. Rimonabant is an inhibitor of the protective action of the endocannabinoid 2-AG use to decrease damage due to the head injury in mice [69]. Similar effects caused by ouabain are seen in THC [70]. Alternatively, via the CB1 receptors pathways, WIN55,2122 or CP-55,940 concentrations protects damage of neurons from hippocampus in rats caused by the action of glutamate [71]. As such however, it was shown that the cannabinoid receptor pathway may not be the only routes that mediate these effects. Consequently, it was reported that action of the compound WIN55,2122 does not involve mechanism with cortical neurons' cannabinoid receptor in cortical neurons under hypoxic conditions [68]. Similar results on the same protective effects 2-AG and anandamide in cultures of cortical neurons were reported as well [72]. There was however a fascinating observation as CBD was reported to lower glutamate-mediated toxicity in cortical neurons of rats when combined with THC [73] with rather no effects on CB1 receptors. However, it might be suggested that these effects could be results of antioxidative effects of these compounds as they have phenolic groups as reported by the researchers in the study.

Studies on cannabinoids have been fascinating yet confusing given its neuroprotective and neurotoxic effects. The mixed reports of neurotoxic and neuroprotective effects of cannabinoids are confusing. However, the fact that less evidence of toxicity is available upon an *in vivo* study where pharmacologically proper concentration and doses of cannabinoids were administered although the results were different in *in vitro* studies when higher doses where administered.

As of 2006, there were no fatal overdoses with cannabis use reported [74]. In a study it was reported that no deaths directly due to acute cannabis use have

ever been reported [75]. The low toxicity of THC, the principal psychoactive constituent of the cannabis plant, ensures that a small amount can enter the body through consumption of cannabis plant and poses no threat of death. It is considered that about 3 g/kg of cannabis is considered the lowest concentration THC that could be harmful to dogs over [76]. According to the Merck Index, [77] 1270 mg/kg and 730 mg/kg are considered the concentrations of THC which causes 50% deaths for rats (i.e. female and male) after administration orally in sesame oil, and 42 mg/kg of THC as lethal dose for rats after inhalation [78]. Consequently, the maximum cannabis to the concentration needed for receptor saturation ratio which is considered to cause intoxication is almost 40,000:1 [79].

Research evaluating the impacts of acutely administered doses of cannabis on executive functioning has generated mixed results (Table **3**) [80]. Most of the studies on CBs have performed on their effects at the molecular and synaptic level. But, the effects of CBs on the dynamics of neural circuits remain ambiguous. Currently Roman *et al*., disentangled the effects of CBs on the functional dynamics of the hippocampal Schaffer collateral synapse by the help of data-driven nonparametric modeling [81]. The researchers recorded multi-unit activity of rats doing a working memory task in control settings and under the impact of exogenously administered THC. It was found that THC left firing rate unchanged and only somewhat reduced theta vacillations. After that, multivariate autoregressive models were subjected to define the dynamical transformation from CA3 to CA1. They exposed that THC aided to isolate CA1 from CA3 by abating feedforward excitation as well as the flow of theta information. The functional isolation was compensated by raised feedback excitation within CA1 that lead to perfect firing rates. Lastly, all of these effects were exposed to be linked with memory deficiencies in the working memory task. By explicating the circuit mechanisms of CBs, these denouements aid to comprehend the cellular and behavioral effects of CBs [81].

CANNABIS AND PSYCHIATRIC DISORDERS

In some cannabis users, a temporary form of drug-induced psychosis can occur. This is sometimes referred to as cannabis psychosis in some psychiatric literature. Research psychiatrists, particularly in Britain, [82] have studied this condition carefully. This condition has been reported to result due to an intake of higher concentrations of such drug particularly with food or beverages, and the condition may persist for some time usually until the accumulated THC has been washed out of the body. Upon hospital admission of the subject due to acute psychosis caused by cannabis, the initial diagnosis could present similar symptoms in schizophrenia and could be a point confusion as the psychosis could have similar schizophrenic symptoms. Such symptoms could include insubordination, loss of control, grandiose identity, disturbed hearing and hallucinations (i.e. including hearing sounds), altercation of emotion and feeling of persecution. Though the similarity of symptoms is much with paranoia in schizophrenia, not all similar symptoms are seen in all patients. Subsequently, this resulted in some researchers proposing a cannabinoid hypothesis of schizophrenia, which suggested that in schizophrenia, certain symptoms might be results from action over-activity of brain's endogenous cannabinoid receptors [83].

The hypothesis that cannabis use might be associated with long-term psychiatric disorders has been studied in a number of studies. The most important evidence for the hypothesis came from a studies in Sweden based on entry to Swedish army by

Table 3: An Outline of Research Denouements on the Effects of Cannabis on Executive Functions [80]

Executive Function Measured	Acute Effects	Residual Effects	Long-Term Effects
Attention/Concentration	Impaired (light users) Normal (heavy users)	Mixed findings	Largely normal
Decision making & risk taking	Mixed findings	Impaired	Impaired
Inhibition/Impulsivity	Impaired	Mixed findings	Mixed findings
Working memory	Impaired	Normal	Normal
Verbal fluency	Normal	Mixed findings	Mixed findings

Note: Acute Effects denotes 0–6 hours after last cannabis use; Residual Effects denotes 7 hours to 20 days after last cannabis use; Long-Term Effects denotes 3 weeks or longer after last cannabis use.

45,5570 conscripts covering their social and drug taking habits [84]. In such case, the cannabis users accounted for a disproportionate number of the 246 cases of schizophrenic illness diagnosed in the overall group on follow-up as a total of 4293 of the conscripts admitted having taken cannabis at least once. There was an increase in occurrence of schizophrenia in individuals previously using cannabis as it is over 2.4 times more than the number of non-cannabis users. Similarly, the relative risk of schizophrenia in the small number of individuals' highly taking cannabis (i.e. heavy users) had increased to 6.0. The results of such studies led to the conclusion by the researchers that cannabis usage could independently be a risk factor for schizophrenia. In alternative reports [81,82,85], Hambrecht and Hafner, [86] reported first episodes of schizophrenia in 232 patients in Germany. The results indicated the rate of schizophrenic risk almost twice of normal controls and approximately 13% had a history of cannabis use previously. Despite the consistency of the results, they could not establish a relationship of cause and effects of cannabis use initially. However it may be concluded that effects of cannabis and schizophrenia could have a single increased risk factor such as nature of personality. Some psychologists and psychiatrists identified some psychological traits known particularly as schizotypy which has been termed to be associated with increased predisposition of psychosis. Additionally, tests on healthy adults indicated individuals using cannabis had higher schizotypy scales scores than non-users [87,88]. The initial reports of a study in Sweden indicated development of schizophrenia in frequent cannabis using patients (i.e. more than 10 times) in addition to using amphetamine which presents schizophrenia like symptoms such as psychosis. Similar predisposition factor to schizophrenia in cannabis users is that they are socially deprived. However, some answers to these claimed criticisms were provided by more consistent check-ups on the Swedish individuals involved in the study [89,90]. This hypothesis that the development of cannabis dependence in young people is associated with increased rates of psychiatric symptoms, both of psychosis and depression and anxiety was strengthened by further reports from New Zealand [91,92], Australia [93] and France [93,94]. However, it remains to be seen, the evidence that the continuous use of cannabis is associated with psychotic symptoms and illness.

Despite more usage of cannabis in the western countries, it might be expected that effects of its use could be increased and the symptoms could displace schizophrenia symptoms in many sufferers, this has not been observed according to reports from epidemiological evidence [95].

CANNABINOIDS ADDICTION, TOLERANCE AND DEPENDENCE

Intricately, as stated earlier cannabis use could promote the condition and symptoms associated with a number of psychotic illnesses. Furthermore, use and taking of cannabis in schizophrenia patients as a form of self-medication will alleviate symptoms such has hallucinations and delusion and could block the action of drugs used to treat the illness [96]. Surprisingly, another study on Swedish patients indicated the use of cannabis could decrease vocal effects and talking abilities caused by schizophrenia [97]. However, it will never be a bad idea to discourage cannabis use in individuals and patients with psychotic illness.

The use of cannabis was previously not regarded as process of drug addiction. Recently, they have been changed in attitudes over the years. According to DSM-IV (American Psychiatric Association, 1994) [98], 'substance dependence' and 'substance abuse' are defined rather than 'addiction'. A number of individuals that are regular users of cannabis could fall into the positive category when the DSM-IV criterion is considered [98].

Just like other brain intoxicants, the effects of cannabis on the brain are via different ways [99]. Cannabis promotes endorphins release in the nucleus accumbens and orbitofrontal cortex causing reward feelings and pleasure. Endorphins are widely known secreted hormones of the brain associated with pleasure feelings and having opioid like effects. Additionally, cannabis additionally acts as a dopamine agonist in the brain, stimulating reinforcement regions in the mesotelencephalic dopamine (DA) system [100,101].

It has been reported that higher intake of cannabis is needed for experiencing similar effects due to developing tolerance with time. The state and nature of individuals including body conditions, temperature, psychomotor activities, pressure and antiemetic properties are related to the occurrence of cannabis tolerance [99,102].

Consequently, the greater period is spent to get the drug and this has led various attempts to block usage. The user experiences intense desire and cravings for cannabis during abstinence periods [100,102,103].

Inconsistent use between doses and discontinuous use are the consequences of cannabis use withdrawal with accompanying symptoms. Feelings of anxiety, fatigue, insomnia, body aches and pains, nausea and nightmares are some of the withdrawal symptoms of cannabis use [103].

Previous studies have indicated that upon withdrawal from cannabis use, the symptoms return after 4 hours, returning to baseline after 4 to 7 days. However, it was reported that the withdrawal symptoms appear within 1 to 3 days and reach maximum stage after 6 days in a recent study. Rather, the most devastating effects and symptoms of withdrawal from cannabis use could last for 4-14 days and depend on a number of factors including concentration of dosage, intake and routes of administration [104].

REGULATORY STATUS OF CANNABINOIDS IN SOCIETY AND CULTURE

In response to use, a lot of countries around the world had set up rules regulating growing, cultivation and transport of cannabis [105,106]. The laws have affected negatively to the growth and cultivation of cannabis particularly for important uses although in other regions, certain condition had allowed the legal handling of cannabis. Additionally, more laws and restrictions have been set in places around Netherland borders including closing shops offering cannabis beverages [107] as well as crackdown against cannabis coffee pushers in Christiana, Copenhagen [108,109]. However in 2012, the Washington Initiative 502 (I-502) was enacted as a state law to officially legalize cannabis in the state of Washington [110]. The similar, law allowing growing and harvesting of cannabis was set in Uruguay, a year after [111], though there was no report of cannabis sale in the country as of August 2014. The Uruguayan cannabis law however described a modification to the legal sale of cannabis in which only licensed cannabis growers would allow to sell although no report of sale was reported or call for application until in 2014, specifically in August [112].

By November 2015, another Asian country reported the legalization of growing and cultivation of cannabis in the state of Uttarakhand principally for industrially based uses [113]. More reports on cannabis came later in 2015 in Australia when a law legalizing cannabis use in scientific researchers was presented by the country's health minister [114]. Furthermore, the country of Canada had been proposing and considering the possibility of legalizing cannabis for similar scientific purposes although no time frame was set for establishing such law [115]. More countries including Czech Republic, [116] Colombia, [117] Ecuador, [118] Mexico, [119], Portugal, [120] and Canada [121] have already legalized cannabis as health concerns have risen in respect to use of drugs.

Recent statistics (2015) in the USA have revealed interesting figures about cannabis use with more than half of the country's population been shown to have used it with further 12 percent of the country's population reported to have used cannabis in the past year while about 7.3% had used cannabis in the past month [122]. Additionally, there was a rise in cannabis intake 2007 from reported 3.5-5.9 % in 2014 and had gone beyond daily cigarette use with daily cannabis use amongst US college students reaching its highest level since records began in 1980 [123].

Cannabis use is more in 18-29 year-olds with these age groups 6 more times likely to use it than 65-year olds and more men (i.e. almost two or more times more) than women all in the USA [124]. In 2015, there was an increase an increase from 38% in 2013 and 33% in 1985 with almost 44% of the US population had already use cannabis in their lifetime [124]. These statistical values could mean that cannabis is by far the most widely used illicit substance [125].

In the USA, the FDA has approved two oral cannabinoids for use as medicine: dronabinol and

Table 4: Typical Pharmaceutical Products of Cannabis [126]

Generic Medication	Brand Name(s)	Country	Licensed Indications
Nabilone	Cesamet	USA, Canada	Antiemetic (treatment of nausea or vomiting) associated with chemotherapy that has failed to respond adequately to conventional therapy
Dronabinol	Marinol		
	Syndros	USA	Anorexia associated with AIDS–related weight loss
Nabiximols	Sativex	Canada, New Zealand, Eight European countries as of 2013	Limited treatment for spasticity and neuropathic pain associated with multiple sclerosis and intractable cancer pain.

nabilone (Table **4**) [126]. Nabiximols, an oromucosal spray derived from two strains of *Cannabis sativa* and containing THC and CBD, is not approved in the United States, but is approved in several European countries, Canada, and New Zealand as of 2013 [126]. Currently in 2018, FDA recommends approval of cannabis-based drug, CBD (Epidiolex) for the treatment of epilepsy [127].

CONCLUSION

Recently cannabis uses have been increased and its stand poised to join alcohol and tobacco as a legal drug. Cannabis use can lead to the development of the copious problems, which takes the form of addiction in severe cases. Substantial studies suggest that cannabis exposure for the period of development can cause long-term or possibly endure adverse changes in the brain including cognitive deficiencies, changed reward system, transformed connectivity, impair memory, attention, and concentration and reduced volume of specific brain regions. So care should be taken for the practical utility of the CBs in the clinical setting.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between all authors. Author MSU designed the study, wrote the protocol, managed the analyses of the study and prepared the draft of the manuscript. Authors SMS, II and AAM managed the literature searches and participated in manuscript preparation. Authors HKH, ZKL, and MU reviewed the scientific contents of the manuscript. All the authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors proclaim no competing interests.

REFERENCES

[1] Vij K. Textbook of forensic medicine & toxicology: Principles & practice. 6th ed., India: Elsevier; 2014.

[2] Russo EB. Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential. 1st ed., The Haworth Integrative Healing Press; Binghamton-USA, 2013; PP 429; 0-7890-1507-2

[3] Newton DE. World energy crisis: a reference handbook, 1st ed.; ABC-CLIO; Santa Barbara-USA,2013.

[4] Benbadis SR, Sanchez-Ramos J, Bozorg A, Giarratano M, Kalidas K, Katzin L, *et al*. Medical marijuana in neurology. Expert Rev Neurother 2014; 14(12): 1453-65. https://doi.org/10.1586/14737175.2014.985209

[5] United Nations Office on Drugs and Crime. World drug report 2015. In: Nations U, editor. New York, 2015.

[6] Anthony S, Fred B, Jennifer D, Sarah D. Marijuana use and support for legal marijuana continue to climb. [cited 2018 February 12]: Available from: https://www.cbsnews.com/news/marijuana-use-and-support-for-legal-marijuana-continue-to-climb/

[7] Mack J. Marijuana use, legal and illegal, is increasing in Michigan. [cited 2018 February 12]: Available from: http://www.mlive.com/news/index.ssf/2017/07/marijuana_use_legal_and_illega.html

[8] Murnion B. Medicinal cannabis. Aust presc 2015; 38(6): 212-15. https://doi.org/10.18773/austprescr.2015.072

[9] Anonymous. Release the strains. Nat Med 2015; 21(9): 963. https://doi.org/10.1038/nm.3946

[10] Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. The J of Hum Pharm and Drg Ther 2013; 33(2): 195-209. https://doi.org/10.1002/phar.1187

[11] Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez *et al*. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015, 33(2): 195-209. https://doi.org/10.1001/jama.2015.6358

[12] Jensen B, Chen J, Furnish T, Wallace M. Medical marijuana and chronic pain: A review of basic science and clinical evidence. Curr pai and Hea Reps 2015: 19(10): 50.

[13] Johns A. Psychiatric effects of cannabis. Br J Psychiatry 2001; 178(2): 116-22. https://doi.org/10.1192/bjp.178.2.116

[14] Riviello RJ. Manual of forensic emergency medicine: A guide for clinicians, 1st ed., Jones & Bartlett Publishers, 2009; 295.

[15] Crippa JA, Zuardi AW, Martín-Santos R, Bhattacharyya S, Atakan Z, McGuire *et al*. Cannabis and anxiety: A critical review of the evidence. Hum Psychopharm: Clin and Exp 2009; 24(7): 515-23. https://doi.org/10.1002/hup.1048

[16] Leweke FM, Mueller JK, Lange B, Rohleder C. Therapeutic potential of cannabinoids in psychosis. Bio Psy 2016; 79(7): 604-12. https://doi.org/10.1016/j.biopsych.2015.11.018

[17] Ksir C, Hart CL. Cannabis and psychosis: A critical overview of the relationship. Curr psy rep 2016; 18(2): 12. https://doi.org/10.1007/s11920-015-0657-y

[18] Gettman J, Kennedy M. Let it grow—the open market solution to marijuana control. Harm Reduct J 2014; 11(1): 32. https://doi.org/10.1186/1477-7517-11-32

[19] United Nations Office on Drugs and Crime. World Drug Report 2010. New York: United Nations Publication, 2010.

[20] Gordon AJ, Conley JW, Gordon JM. Medical consequences of marijuana use: a review of current literature. Curr Psy Rep 2013; 15(12): 419. https://doi.org/10.1007/s11920-013-0419-7

[21] American College of Obstetricians and Gynecologists. Marijuana use during pregnancy and lactation. Committee Opinion. Obs and Gyn 2015; 126(1): 234-8.

[22] Gunn JK, Rosales CB, Center KE, Nuñez A, Gibson SJ, Christ C, *et al*. Prenatal exposure to cannabis and maternal

and child health outcomes: A systematic review and meta-analysis. BMJ Open 2016; 6(4): e009986. https://doi.org/10.1136/bmjopen-2015-009986

[23] Conner SN, Bedell V, Lipsey K, Macones GA, Cahill AG, Tuuli MG. Maternal marijuana use and adverse neonatal outcomes. Obs & Gyn 2016; 128(4): 713-23. https://doi.org/10.1097/AOG.0000000000001649

[24] Subbaraman MS. Can cannabis be considered a substitute medication for alcohol? Alco and Alcoh 2014; 49(3): 292-8. https://doi.org/10.1093/alcalc/agt182

[25] Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment—a systematic review. J of Med Tox 2017; 13(1): 71-87. https://doi.org/10.1007/s13181-016-0595-z

[26] Uddin MS, Amran MS. Cannabinoid hyperemesis: An erratic syndrome linked with Cannabis abuse. J Psychiatry 2018; 21(2): 1-2. https://doi.org/10.4172/2378-5756.1000e116

[27] Felder CC, Joyce KE, Briley EM, Mansouri J, Mackie K. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Mol Pharmacol 1995; 48: 443-450.

[28] Pinterest.com. CB1 receptors in brain. [cited 2018 February 12]: https://www.pinterest.com.mx/pin/359443613992533228

[29] Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008; 153: 199-215. https://doi.org/10.1038/sj.bjp.0707442

[30] Iversen L. Cannabis and the brain. Br 2003; 126: 1252-1270. https://doi.org/10.1093/brain/awg143

[31] Limebeer CL, Rock EM, Mechoulam R, Parker LA. The anti-nausea effects of CB1 agonists are mediated by an action at the visceral insular cortex. Br J Pharmacol 2012; 167: 1126-1136. https://doi.org/10.1111/j.1476-5381.2012.02066.x

[32] Scholastic. The Science of Marijuana: How THC Affects the Brain. [cited 2018 February 12]: Available from: http://headsup.scholastic.com/students/the-science-of-marijuana

[33] Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. Pharmacol Ther 1997; 74(2):129-80. https://doi.org/10.1016/S0163-7258(97)82001-3

[34] Benson Jr JA, Watson Jr SJ, Joy JE. Marijuana and medicine; The National Academies Press: Washington DC, USA, 1999; 288.

[35] Eubanks LM, Rogers CJ, Beuscher IV AE, Koob GF, Olson AJ, Dickerson TJ, *et al*. A molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharm 2006; 3(6): 773-7. https://doi.org/10.1021/mp060066m

[36] Reggio PH. Endocannabinoid binding to the cannabinoid receptors: What is known and what remains unknown. Curr Med Chem 2010; 17(14): 1468-1486. https://doi.org/10.2174/092986710790980005

[37] Sherman C, Writer NN. The defining features of drug intoxication and addiction can be traced to disruptions in cell-to-cell signaling. NIDA Notes: NIH, NIDA 2007; 21(4).

[38] Osborne GB, Fogel C. Understanding the motivations for recreational marijuana use among adult Canadians. Subst Use Misuse 2008; 43(3-4): 539-72. https://doi.org/10.1080/10826080701884911

[39] Shrivastava A, Johnston M, Terpstra K, Bureau Y. Pathways to psychosis in Cannabis abuse. Clin Schizophr Relat Psychoses 2013; 9(1): 30-5. https://doi.org/10.3371/CSRP.SHJO.030813

[40] Niesink RJ, van Laar MW. Does cannabidiol protect against adverse psychological effects of THC? Front Psychiatry 2013, 4: 130. https://doi.org/10.3389/fpsyt.2013.00130

[41] Shufman E, Lerner A, Witztum E. Depersonalization after withdrawal from cannabis usage. Euro PMC 2005, 144(4): 249.

[42] Johnson BA. Psychopharmacological effects of cannabis. Br J Hosp Med 1990; 43(2): 114-6.

[43] Barceloux DG. Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants. John Wiley & Sons: New York; 2012. https://doi.org/10.1002/9781118105955

[44] Atakan Z. Cannabis, a complex plant: Different compounds and different effects on individuals. Ther Adv Psychopharmacol 2012; 2(6): 241-54. https://doi.org/10.1177/2045125312457586

[45] Kogan NM, Mechoulam R. Cannabinoids in health and disease. Dialogues Clin Neurosci 2007; 9(4):413.

[46] Grotenhermen F, Müller-Vahl K. The Therapeutic Potential of Cannabis and Cannabinoids. Dtsch Arztebl Int 2012; 109(29-30): 495-501. https://doi.org/10.3238/arztebl.2012.0495

[47] Hill KP. Medical Marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. JAMA 2015; 313(24): 2474-83. https://doi.org/10.1001/jama.2015.6199

[48] Thompson AE. Medical Marijuana. JAMA 2015; 313(24): 2508. https://doi.org/10.1001/jama.2015.6676

[49] Grotenhermen F, Müller-Vahl K. The therapeutic potential of cannabis and cannabinoids. Dtsch Arztebl Int 2012; 109(29-30): 495. https://doi.org/10.3238/arztebl.2012.0495

[50] American Academy of Neurology. Medical marijuana in certain neurological disorders. [cited 2018 February 12]: Available from: https://www.aan.com/Guidelines/Home/GetGuidelineContent/650

[51] Dornbush RL, Freedman AM, Fink M. Chronic cannabis use. Ann N Y Acad Sci 1976; 282: 1-430.

[52] Filbey FM, Aslan S, Calhoun VD, Spence JS, Damaraju E, Caprihan A, Segall J. Long-term effects of marijuana use on the brain. Proc Natl Acad Sci U S A. 2014 Nov 25; 111(47): 16913-8. https://doi.org/10.1073/pnas.1415297111

[53] Solowij N. Cannabis and cognitive functioning. Cambridge: Cambridge University Press; 1998; 92-102. https://doi.org/10.1017/CBO9780511526824

[54] Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001; 58(10): 909-15. https://doi.org/10.1001/archpsyc.58.10.909

[55] Hollister LE. Health aspects of cannabis. Pharmacol Rev 1986; 38: 1–20.

[56] Block RI, O'Leary DS, Ehrhardt JC, Jean CA, Ghoneim MM, Stephan A, *et al*. Effects of frequent marijuana use on brain tissue volume and composition. Neuroreport 2000; 11: 491-6. https://doi.org/10.1097/00001756-200002280-00013

[57] Scallet AC, Uemura E, Andrews A, Ali SF, Mcmillan DE, Paule *et al*. Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). Brain Res 1987; 436: 193-8. https://doi.org/10.1016/0006-8993(87)91576-9

[58] Landfield PW, Cadwallader LB, Vinsant S. Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. Brain Res 1988; 443: 47-62. https://doi.org/10.1016/0006-8993(88)91597-1

[59] Chan PC, Sills RC, Braun AG, Haseman K, Bucher JR. Toxicity and carcinogenicity of delta 9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice. Fundam Appl Toxicol 1996; 30: 109-17. https://doi.org/10.1006/faat.1996.0048

[60] Harper JW, Heath RG, Myers WA. Effects of cannabis sativa on ultrastructure of the synapse in monkey brain. J Neurosci Res 1977; 3: 87-93. https://doi.org/10.1002/jnr.490030202

[61] Heath RG, Fitzjarrell AT, Fontana CJ, Garey RE. Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys. Biol Psychiatry 1980; 15: 657-90.

[62] Scallet AC. Neurotoxicology of cannabis and THC: A review of chronic exposure studies in animals. Pharmacol Biochem Behav 1991; 40: 671-6. https://doi.org/10.1016/0091-3057(91)90380-K

[63] Downer E, Boland B, Fogarty M, Campbell V. Delta 9-tetrahydrocannabinol induces the apoptotic pathway in cultured cortical neurones via activation of the CB1 receptor. Neuroreport 2001; 12: 3973-8. https://doi.org/10.1097/00001756-200112210-00024

[64] Chan GC, Hinds TR, Impey S, Storm DR. Hippocampal neurotoxicity of delta 9-tetrahydrocannabinol. J Neurosci 1998; 18: 5322-32. https://doi.org/10.1523/JNEUROSCI.18-14-05322.1998

[65] Sánchez C, Galve-Roperh I, Canova C, Brachet P, Guzmán M. Delta 9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. FEBS Lett 1998; 436: 6-10. https://doi.org/10.1016/S0014-5793(98)01085-0

[66] Galve-Roperh I, Sánchez C, Cortés ML, del Pulgar TG, Izquierdo M, Guzmán M. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. Nat Med 2000; 6: 313-9. https://doi.org/10.1038/73171

[67] Guzmán M, Sánchez C, Galve-Roperh I. Control of the cell survival/death decision by cannabinoids. J Mol Med 2001; 78: 613-25. https://doi.org/10.1007/s001090000177

[68] Nagayama T, Sinor AD, Simon RP, Chen J, Graham SH, Jin K, *et al*. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. J Neurosci 1999; 19: 2987-95. https://doi.org/10.1523/JNEUROSCI.19-08-02987.1999

[69] Panikashvili D, Simeonidou C, Ben-Shabat S, Hanuš L, Breuer A. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature 2001; 413: 527-31. https://doi.org/10.1038/35097089

[70] Van der Stelt M, Veldhuis WB, Bär PR, Veldink GA, Vliegenthart JF, Nicolay K. Neuroprotection by delta-9-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced *in vivo* excitotoxicity. J Neurosci 2001; 21: 6475-9. https://doi.org/10.1523/JNEUROSCI.21-17-06475.2001

[71] Shen M, Thayer SA. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. Mol Pharmacol 1998; 54: 459-62. https://doi.org/10.1124/mol.54.3.459

[72] Sinor AD, Irvin SM, Greenberg DA. Endocannabinoids protect cerebral cortical neurons from *in vitro* ischemia in rats. Neurosci Lett 2000; 278: 157-60. https://doi.org/10.1016/S0304-3940(99)00922-2

[73] Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)delta 9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci USA 1998; 95: 8268-73. https://doi.org/10.1073/pnas.95.14.8268

[74] Calabria B, Degenhardt L, Hall W, Lynskey M. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug Alcohol Rev 2010; 29(3): 318-30. https://doi.org/10.1111/j.1465-3362.2009.00149.x

[75] Ashton CH. Pharmacology and effects of cannabis: a brief review. Br J Psychiatry 2001; 178(2): 101-6. https://doi.org/10.1192/bjp.178.2.101

[76] Fitzgerald KT, Bronstein AC, Newquist KL. Marijuana poisoning. Top Companion Anim Med 2013; 28(1): 8-12. https://doi.org/10.1053/j.tcam.2013.03.004

[77] O'Neil, Maryadele J. The Merck index : an encyclopedia of chemicals, drugs, and biologicals. 12th ed., New Jersey. Cambridge, UK : Royal Society of Chemistry; 2013, 234.

[78] Erowid. Cannabis: Legal Status. [cited 2018 February 12]: Available from: https://erowid.org/plants/cannabis/cannabis_law.shtml

[79] Mikuriya TH. Historical aspects of cannabis sativa in western medicine. New Physician. 1969; 18: 902-8.

[80] Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med 2011; 5(1): 1-8. https://doi.org/10.1097/ADM.0b013e31820c23fa

[81] Sandler RA, Fetterhoff D, Hampson RE, Deadwyler SA, Marmarelis VZ. Cannabinoids disrupt memory encoding by functionally isolating hippocampal CA1 from CA3. PLoS Comput Biol 2017; 13(7): e1005624. https://doi.org/10.1371/journal.pcbi.1005624

[82] Johns A. Psychiatric effects of cannabis. Br J Psychiatry 2001; 178: 116-22. https://doi.org/10.1192/bjp.178.2.116

[83] Emrich HM, Leweke FM, Schneider U. Towards a cannabinoid hypothesis of schizophrenia: cognitive impairments due to dysregulation of the endogenous cannabinoid system. Pharmacol Biochem Behav 1997; 56: 803-7. https://doi.org/10.1016/S0091-3057(96)00426-1

[84] Andréasson S, Engström A, Allebeck P, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 1987; 2: 1483-5. https://doi.org/10.1016/S0140-6736(87)92620-1

[85] Mathers DC, Ghodse AH. Cannabis and psychotic illness. Br J Psychiatry 1992; 161: 648-53. https://doi.org/10.1192/bjp.161.5.648

[86] Hambrecht M, Hafner H. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. Aust NZ J Psychiatry 2000; 34: 468-75. https://doi.org/10.1080/j.1440-1614.2000.00736.x

[87] Williams JH, Wellman NA, Rawlins JNP. Cannabis use correlates with schizotypy in healthy people. Addiction 1996; 91: 869-77. https://doi.org/10.1111/j.1360-0443.1996.tb03581.x

[88] Skosnik PD, Spatz-Glenn L, Park S. Cannabis use is associated with schizotypy and attentional disinhibition. Schizophr Res 2001; 48: 83-92. https://doi.org/10.1016/S0920-9964(00)00132-8

[89] Andreasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis. Acta Psychiatr Scand 1989; 79: 505-10. https://doi.org/10.1111/j.1600-0447.1989.tb10296.x

[90] Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ 2002; 325: 1199. https://doi.org/10.1136/bmj.325.7374.1199

[91] Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002; 325: 1212-3. https://doi.org/10.1136/bmj.325.7374.1212

[92] Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med 2003; 33: 15-21. https://doi.org/10.1017/S0033291702006402

[93] Patton GC, Coffey C, Carlin JB, *et al*. Cannabis use and mental health in young people: cohort study. BMJ 2002; 325: 1195-8. https://doi.org/10.1136/bmj.325.7374.1195

[94] Verdoux H, Gindre C, Sorbara F, Tournier M, Swendsen JD. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. Psychol Med 2003; 33: 23-32. https://doi.org/10.1017/S0033291702006384

[95] Thornicroft G. Cannabis and psychosis. Is there epidemiological evidence for an association? Br J Psychiatry 1990; 157: 25-33. https://doi.org/10.1192/bjp.157.1.25

[96] Linzen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 1994; 51: 273-9. https://doi.org/10.1001/archpsyc.1994.03950040017002

[97] Peralta V, Cuesta MJ. Influence of cannabis abuse on schizophrenic psychopathology. Acta Psychiatr Scand 1992; 85: 127-30. https://doi.org/10.1111/j.1600-0447.1992.tb01456.x

[98] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. DSM-IV. 4th ed. Washington (DC): American Psychiatric Association; 1994.

[99] Sharma P, Murthy P, Bharath MM. Chemistry, metabolism and toxicology of cannabis: Clinical implications. Iran J Psychiatry 2012; 7: 149-156.

[100] Gold MS, Miller NS. Seeking drugs/alcohol and avoiding withdrawal: the neuroanatomy of drive states and withdrawal. Psychiatr Ann 1992; 22(8): 430-5. https://doi.org/10.3928/0048-5713-19920801-09

[101] Ellgren M, Spano SM, Hurd YL. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. Neuropsychopharmacology 2007; 32: 607-615. https://doi.org/10.1038/sj.npp.1301127

[102] Nocon A, Wittchen HU, Pfister H, Zimmermann P, Lieb R. Dependence symptoms in young cannabis users? A prospective epidemiological study. J Psychiatr Res 2006; 40: 394-403. https://doi.org/10.1016/j.jpsychires.2005.07.011

[103] Lamarine RJ. Marijuana: Modern medical chimaera. J Drug Educ 2012; 42: 1-11. https://doi.org/10.2190/DE.42.1.a

[104] Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers 2007; 4: 1770-1804. https://doi.org/10.1002/cbdv.200790152

[105] Degenhardt L, Ferrari AJ, Calabria B, Hall WD, Norman RE, McGrath J *et al*. The Global Epidemiology and Contribution of Cannabis Use and Dependence to the Global Burden of Disease: Results from the GBD 2010 Study. Brody JP, ed. PLoS One. 2013;8(10):e76635.

[106] David Levinson. Encyclopedia of Crime and Punishment. SAGE Publications. 2002, 572.

[107] Wikipedia. Cannabis (drug). [cited 2018 February 12]: Available from: http://enacademic.com/dic.nsf/enwiki/727377/Cannabis_%28drug%29

[108] EMCDDA. Cannabis reader: Global issues and local experiences, Perspectives on Cannabis controversies, treatment and regulation in Europe, 2008; 157. [cited 2018 February 12]: Available from: http://www.emcdda.europa.eu/publications/monographs/cannabis_en

[109] Frank VA. Danish drug policy-Shifting from liberalism to repression. Drugs and Alcohol Today 2008; 8(2): 26-33. https://doi.org/10.1108/17459265200800015

[110] Myers LL. Marijuana goes legal in Washington state amid mixed messages. [cited 2018 February 12]: Available from: https://www.reuters.com/article/us-usa-marijuana-washington/marijuana-goes-legal-in-washington-state-amid-mixed-messages-idUSBRE8B506L20121206

[111] Vicky Baker. "Marijuana laws around the world: what you need to know". [cited 2018 February 12]: Available from: https://www.theguardian.com/travel/2013/dec/11/uruguay-marijuana-laws-around-world

[112] Rojo M. Uruguay pharmacies start selling cannabis straight to consumers. [cited 2018 February 12]: Available from: https://www.theguardian.com/world/2017/jul/19/uruguay-marijuana-sale-pharmacies

[113] Abraham B. Uttarakhand To Become First Indian State To Legalise Cannabis Cultivation. [cited 2018 February 12]: Available from: https://www.indiatimes.com/news/india/uttarakhand-to-become-first-indian-state-to-legalise-cannabis-cultivation-247769.html

[114] Alchimia Grow Shop'sofficial blog. Medical marijuana news, December 2015, Australia will allow to grow cannabis for medical studies. [cited 2018 February 12]: Available from: https://www.alchimiaweb.com/blogen/medical-marijuana-news-december-2015/

[115] Kane L. Canadians facing pot charges in limbo, while Liberals work on legalization. [cited 2018 February 12]: Available from: https://www.theglobeandmail.com/news/british-columbia/canadians-facing-pot-charges-in-limbo-while-liberals-work-on-legalization/article27935465/

[116] Anonymous. Drug Policy of the Czech Republic. [cited 2018 February 12]: Available from: http://www.popflock.com/learn?s= Drug_policy_of_the_Czech_Republic

[117] Castaneda JG. The summit of muted intentions. [cited 2018 February 12]: Available from: http://www.aljazeera.com/indepth/opinion/2012/03/201232712571428188O.html

[118] Anonymous. Ecuador: Aprueban tenencia de drogas para consume. [cited 2018 February 12]: Available from: https://www.revolvy.com/main/index.php?s=El%20Comercio%20(Ecuador)

[119] Jorge HT, and Angles ZC. Mexico: The Law Against Small-Scale Drug Dealing. A Doubtful Venture, Series on Legislative Reform of Drug Policies. Legislative, Nr 3, 2009.

[120] European Monitoring Centre for Drugs and Drug Addiction. Drug policy profiles — Portugal. [cited 2018 February 12]: Available from: http://www.emcdda.europa.eu/publications/drug-policy-profiles/portugal_en

[121] Anonymous. Marijuana. [cited 2018 February 12]: Available from: http://www.popflock.com/learn?s=Marijuana

[122] Motel S. 6 facts about marijuana. [cited 2018 February 12]: Available from: http://www.pewresearch.org/fact-tank/2015/04/14/6-facts-about-marijuana/

[123] Wadley J. Daily marijuana use among college students highest since 1980. [cited 2018 February 12]: Available from: http://ns.umich.edu/new/releases/23088-daily-marijuana-use-among-u-s-college-students-highest-since-1980

[124] McCarthy J. More Than Four in 10 Americans Say They Have Tried Marijuana. Available from: http://news.gallup.com/poll/184298/four-americans-say-tried-marijuana.aspx. Accessed on 16 February 2018.

[125] Jonathan PC, Angela H, Beau K, Mark ARK. Marijuana Legalization: What Everyone Needs to Know. [cited 2018 February 12]: Available from: https://global.oup.com/academic/product/marijuana-legalization-9780199913718?cc=us&lang=en&#

[126] Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy. 2013; 33(2): 195-209. https://doi.org/10.1002/phar.1187

[127] Scientific American. Panel recommends FDA approval of epilepsy drug derived from marijuana [cited 2018 April 23]: Available from: https://www.scientificamerican.com/article/panel-recommends-fda-approval-of-epilepsy-drug-derived-from-marijuana/?sf187440701=1

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