

## *Cannabis sativa* – A matter of physical, mental, and social health

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### ABSTRACT

Several studies show that chronic marijuana use opens doors to several disorders, especially neuropsychiatric disorders. Others consider cannabinoids to be promising in therapeutic practice. Here, we present a literature review, based on selected publications on the Medline and Scielo databases, on health and cannabis use. This review aims to assist health professionals and students in understanding the growing number of marijuana users who look for help in outpatient clinics and offices. Therefore, there is an increase in the frequency of hospital admissions for psychotic disorders in clinics and specific treatment institutions. Research over the past 35 years has shown that marijuana use promotes only momentary anxiolysis. This drug alone or in combination with cigarette, when consumed for a long term, can deteriorate the user's intellectual capacity, academic performance, and professional achievements and finally results in social isolation. The current situation demonstrates that cannabis usage is a public health issue that needs to be addressed in health policy because the majority of users get sick and lose their ability to work.

**Key words:** *Adverse effects, Cannabinoids, Cannabis sativa, Drug addiction*

**C**annabis is a plant that belongs to angiosperm group, originating in Central and South Asia, and brought to the Western world in the late 19<sup>th</sup> century. Today, its cultivation, physiological effects, ability to generate chemical dependency, and possible neuropsychiatric damage have been the subject of great debate. However, only few people are aware that there are three types of cannabis, each with a unique chemical composition and use: *Cannabis ruderalis* (CR), *Cannabis sativa* (CS), and *Cannabis indica* (CI) [1]. The *Cannabis* plant contains more than 700 chemical substances such as terpenoids, polyphenols, cannabinoids, and flavonoids [2], and more than 100 phytocannabinoids with varying pharmacological and toxicological effects [3].

CR, also known as hemp, provides a type of fiber that is employed in textile, paper, and rope industries. Oil extracted from the hemp seed has been applied in mechanical equipment, cosmetics, and paint manufacturing industries [1,3,4]. Due to its high delta-9-tetrahydrocannabinol (THC) content, CS and CI have a long history of being utilized for both recreational and therapeutic purposes. This cannabinoid has a high psychoactive power that is primarily responsible for the toxicity of these cannabis varieties [2,5].

CS, also known as *marijuana*, is the most used illicit psychoactive drug in the world [6-9], and is now common among adolescents [10-13]. The sensation caused by this drug, which makes its consumption so high, results from acute intoxication by THC [8,14].

In addition to THC, the known cannabinoids from CS include Cannabidiol (CBD), tetrahydrocannabinolic acid, THC, cannabinol (CBN), cannabidiolic acid, cannabigerol, cannabidivarin, and cannabidibutol. Almost minimal information is currently available on the components of CS, with the exception of the THC and CBD. Given the cumulative effects that could result from the lipophilicity of several substances found in this plant, this could pose a serious threat to one's health [14,15]. It is known that CBD has therapeutic properties and no psychoactive effect therapeutic properties and no psychoactive effect [9,14]. However, its adverse effects are not fully understood [9,16]. Given the potential therapeutic benefits that some cannabinoids may offer, searches have been made for substances that can neutralize their potential acute side effects (hypothermia, tachycardia, etc.) [17,18].

Cannabinoids, primarily THC, can easily cross organic barriers and accumulate in tissues due to the high lipophilic content. Furthermore, cannabinoids may bind to serum albumin since spectrofluorimetric studies have clearly shown that the high lipophilicity of an exogenous agent favors its interaction with this protein, which starts to function as a plasma reservoir for this [19-21]. Thus, marijuana dependence prolongs the body's exposure to its constituents, and among them, there are oxidants and antioxidant enzyme inhibitors, such as THC [22].

In "heavy" marijuana users, THC can be detected in the blood even after 2 months since the last use and may be present incessantly in smokers who smoke one cigarette per week [6,14]. This is a big difference between marijuana and alcohol

dependence, as the plasma level of ethanol vanishes 24 h after consumption. Many CS users deny having an addiction since they may go days without smoking, yet this satiety may be caused by the slow release of THC that has been stored in tissues and plasma proteins [23,24].

Unfortunately, the use of marijuana among adolescents has increased significantly in recent decades. In the United States, application of hierarchical age-period-cohort logistic regression models showed a substantial increase in marijuana use among adolescents from 1991 to 2018. In addition, there was a clear age-related increase in the drug consumption [25]. There are also hints that teen cannabis use has increased in various European nations. Between 2014 and 2018, the proportion of those in England reporting cannabis use climbed from 3.9 to 4.4% [26].

It's crucial to keep in mind that adolescence is a time when the nervous system is experiencing intensive, ongoing, and comprehensive neurological growth, making it especially susceptible to the damaging effects of drugs [27,28]. In adolescent rats, THC was able to change the morphology of neurons in the dentate gyrus and decreased the number of dendritic branches [29]. This would explain the memory impairment and cognitive decline with prolonged and early-onset marijuana use. Dendritic changes were also observed in rats treated with the synthetic cannabinoid WIN 55.212-2 [30].

Danielson *et al.* [13] attributed unemployment and the need for social assistance in a group of Swedish men to the intense use of cannabis during late adolescence. They could not identify any other type of problem (health, social, or behavioral) that would justify the unfavorable conditions of those men. In addition to the detrimental impact of marijuana, the decriminalization and legalization of marijuana use in the US have been blamed for the rise in illnesses among young people as it downplays the harmful consequences of this drug and disrupts public health policy [8,10].

Carranza in 2012 [31] came to the conclusion that legalizing marijuana should be discouraged but that its application through the enteral route to alleviate the suffering of terminally ill patients can be useful based on the pharmacological analysis, medicinal properties, and known risks of marijuana. In fact, the liberation of illegal drug use is a matter of great complexity, shrouded in controversies and contradictions [32].

An aggravating fact is the increase in THC concentrations that has been discovered in samples of cannabis resins seized by the authorities since 1980 [7,33,34]. About 3-fold increase in the THC: CBD ratio has already been found in samples analyzed between 2000 and 2017 in Danish forensic laboratories [35]. However, while having a crucial role in CSs level of toxicity, the laws governing the legalization of marijuana place little weight on this ratio [7].

Here, in this article, we seek to gather evidence that allows us to draw a profile of CS actions in the user's body, especially in the nervous system, based on an analysis of material published from 2020 to 1985. This article aims to provide information to medical professionals and students that can offer explanations for what has been seen in medical offices and clinics, particularly in

psychiatry and psychology, where the number of marijuana users seeking help grows every year. It also aims to address the rising number of hospital admissions for psychotic disorders and in facilities for the treatment of chemical dependency.

## THC AND ITS RECEPTORS

The receptors that THC binds are expressed to be modulated by substances that are synthesized by the body, such as N-arachidonyl ethanolamine or anandamide (ANA) and 2-arachidonylglycerol (ANG) [14,36]. However, because they were found in THC research, these receptors were given the name "cannabinoids," and their innate ligands were given the name "endocannabinoids" or "endogenous cannabinoids." Like all endogenous modulators, ANA and ANG are released when needed in response to endogenous signaling [14,15]. However, the use of marijuana leads to the action of its components on receptors for ANA and ANG, among others, without any endogenous signaling.

At present, two types of cannabinoid receptors are known: Type 1 (CB1) and type 2 (CB2). There is 45% similarity in the nucleotide sequences of CB1 and CB2. Both are adenylyl cyclase inhibitors [36], linked to GIRK potassium channels and mitogen-activated protein kinases (extracellular stimuli). Protein kinases are involved in the regulation of several cellular activities, including gene expression, mitosis, and apoptosis [37], but CB1 also inhibits voltage-operated calcium channels [38]. The psychoactive and analgesic effects of THC and the development of dependence are mediated by CB1 receptors.

CB1 receptors and their CB1A variant are predominant in the brain, especially in the frontal lobe, hippocampus and striatum of cerebrum, and cerebellum. CB2 is more frequent in spleen, tonsils, thymus, lymphocytes, monocytes, mast cells, and microglia [38].

Calcium channels inhibited by CB1 are of types T, N, and P/Q, which play an important role in neurophysiology by acting on neurotransmitter release and depolarization of the post-synaptic neuron membrane [39-41]. T channels play an important role in rhythmic discharges of generalized and absence epileptic seizures. Several neurological disorders are related to P/Q channel dysfunctions, including Alzheimer's disease, ataxia, and migraine [39,42-44].

It is possible that some exogenous cannabinoids interact equally with both receptors, but THC acts primarily on CB1, and its response depends on the plasma concentration [45,46].

ANA and ANG are CB1 receptor ligands. These ligands and their receptors form the central cannabinoid neuromodulator system. The endocannabinoid ANA is released by neurons after depolarization through a calcium-dependent mechanism that requires cleavage of a phospholipid present in neuronal membranes [14]. Similar to endocannabinoids, exocannabinoids act on CB1 by inhibiting presynaptic membrane, calcium channels, and by promoting the opening of potassium channels. This causes a reduction in release of neurotransmitters and synaptic transmission [6,38,47].

Tolerance and dependence involve alterations in the drug-receptor interaction. Dependence, when late, involves a decrease

in the number of receptors or changes in the signal transmission pathway of other signaling molecules, which may result from modifications at the gene level.

## CANNABIS SATIVA AND ITS IMMEDIATE EFFECTS

By acting on the peripheral nervous system, and somatic and neurovegetative synapses, CS can influence the functioning of striated and smooth muscles, and organs in general. Inhibition of salivary secretion and xerostomia, reduction of gastric acid secretion, and excessive tearing are commonly noted [48-50].

The plasma concentration of THC reaches its peak within a few minutes of inhalation in the lungs. Due to its high lipophilicity, THC passes through more vascularized tissues including the brain, heart, kidney, and liver but accumulates in less vascularized tissues like adipose [14,23]. This accumulation varies among people and determines how long the drug remains in the body, because THC returns to the blood even during abstinence [51,52].

The psychotropic effects that can occur after a drag on a marijuana cigarette are varied. A sense of elation (moderate euphoria) often arises within seconds to a few minutes, develops to its peak in 15–30 min, and begins to wane in 2–4 h, however, it can persist up to 5 h. [14,51]. The oral route has comparatively delayed psychotropic effects, beginning 30–90 min after delivery, peaking in 2 h, and continuing between 4 and 12 h, depending on the dose [51].

In elation, there may be a feeling of pleasure, decreased anxiety, relaxation, and increased sociability. Conversely, feelings of displeasure, anguish, and anxiety may arise, with symptoms of panic and isolation, in addition to detectable effects by subjective measures [12,51,53]. During intoxication, a variety of psychic effects can occur, such as loss of time-spatial orientation, impairment of motor coordination, delay in sensory perception, decreased attention and concentration, with impairment in memorization and intellectual and cognitive functions. There is a possibility of the occurrence of psychotic symptoms, such as persecutory or grandiosity delusions and depersonalization [14,54].

In addition to psychotic effects, tachycardia, arterial hypertension, and reduced pupillary reflex can occur. However, at higher doses, marijuana can cause hypotension, tachypnea, conjunctival hyperemia, hyperphagia, lethargy, and reduced muscle reflexes [14,53-56]. In the post-elation phase, lethargy, decreased mental concentration, reduced motor reflexes, drowsiness, and spontaneous laughter may occur. This phase can last for 24 h as THC that is retained in the tissues returns to circulation [14,23,53].

Hyperphagia caused by CS occurs due to its action on hypothalamic cannabinoid receptors and on endocrine and digestive mechanisms, for example, the reduction of leptin release [45,56,57]. The centers that regulate eating behavior are located in hypothalamus, and leptin is a hormone produced in the adipose tissue that acts in this area of the brain and reduces appetite [58].

THC and other cannabinoids have the advantageous effect of reducing pain by acting on the brainstem and regulating the spinal cord's rostral ventromedial neuronal activity [47]. Meng *et al.* showed that centrally acting analgesic cannabinoids act in the same circuits as opioid analgesics, but the mechanisms of action seem to be distinct [59]. However, these authors warn that "inactivation of the rostral ventromedial medulla prevents analgesia, but not motor deficits produced by systemically administered cannabinoids."

Another cannabinoid effect that can be positive is hypothermia, which also seems to be due to action in sites in the brainstem. Intravenous administration of THC in cats was able to block tremors induced by artificial cooling in the pre-optic area of the hypothalamus. Such cooling was generated by a temperature regulating device (thermode) implanted in that area [60], where the temperature reduction generates impulses sent to the brainstem, which triggers responses to conserve body temperature [58].

## CANNABIS SATIVA AND ITS LONG-TERM EFFECTS

### Changes in Gene Expression and at the Gene Level

It is well known that CS elements have the capacity to influence both protein gene expression and gene activity. This highlights the possible depth and extent of the action of cannabinoids in cells, especially in young humans. A study involving 88 marijuana users and 147 non-users showed a positive relationship between the use of this drug and variations in the gene encoding the CB1 receptor in the dorsolateral prefrontal cortex, related to working memory [61].

Prenatal exposure of rats to THC affects the gene expression and activity of the enzyme tyrosine hydroxylase in brain neurons [62], and the gene expression of neuropeptides such as substance P and enkephalin. In rats treated with THC, a significant increase in mRNA involved in synthesis of these two neuropeptides was observed in striatal neurons [23].

In airways, in addition to DNA replication, marijuana induces transcriptional responses in epithelial cells similar to those caused by tobacco smoke [63]. In those cells, THC reduces the expression of the gene related to the formation of the anionic transport protein cystic fibrosis transmembrane regulator (CFTR) [64]. This protein is responsible for transporting chloride and bicarbonate across the apical membrane of airway epithelial cells, playing a fundamental role in regulating epithelial secretion and absorption processes. It is important to mention that this type of protein is present in epithelial cells of exocrine glands, such as the sweat glands, pancreas, glands of the large intestine, testicles, and vas deferens.

### Neuropsychiatric Disorders

The chronic use of marijuana increases the risk of developing neuropsychiatric disorders, such as cognitive difficulties, memory deficits, and psychotic, depressive, and anxiety disorders [2,65-70].

Although it was considered as a “soft” drug for a long time, Angela Ameri [14] drew attention to the discovery of neuronal apoptosis induced by THC in the hippocampus of rats, in addition to the retraction of neurons and DNA fragmentation. Studies in several countries have demonstrated that frequent and prolonged marijuana use leads to psychological and chemical dependence, in addition to neurophysiological damage, thereby opening the way for serious psychiatric and neurological diseases [17,71-77]. There is a suggestion that altered levels of endocannabinoids in cerebrospinal fluid and/or blood may play a role in the etiology of schizophrenia [77]. Several studies show changes in cannabinoid receptors resulting from the use of CS [77,78]. Furthermore, increased oxidative stress responses in neurons were detected in 45 patients dependent on this drug, suggesting impairment of the natural antioxidant system [22].

Due to its anxiolytic effect during the first 2 h after a drag, social anxiety has been identified as a condition that leads to the use and dependence of marijuana [12,69]. There is a suggestion that this effect may be related to the cannabinoid action in the midbrain, more precisely in the periaqueductal gray matter [79]. However, this drug is strongly contraindicated for these cases, as its continued use can lead to anxiety and mood disorders [11,80-81]. Gobbi *et al.* [82] pointed out that the marijuana use in adolescence increases the risk of developing depression and the probability of suicide in young people.

In France, a study [80] carried out at the Lariboisière Hospital, from January 2004 to December 2009, involving 207 young patients undergoing treatment, found that 97.1% of them were dependent on marijuana for a long time. This suggested the presence of high comorbidity with anxiety and mood disorders. Among these patients, 19.4% had a history of suicide attempt. The most frequent anxiety disorders in those patients, in descending order of frequency, were social phobia, generalized anxiety, panic, agoraphobia, obsessive-compulsive disorder, and post-traumatic stress. Major depressive disorder was the most prevalent mood condition, followed by dysthymia, mania, and hypomania.

A Portuguese follow-up research at public hospitals from 2000 to 2015 revealed a rise in hospitalizations for psychotic disorders, which was attributed to the rising number of marijuana users who sought treatment [83].

According to a study conducted in Spain with 379 transgender patients at the University of Malaga [84], chronic marijuana users tend to be older and more victimized than those who have never used the substance, which makes them more likely to seek treatment at the Department of Mental Health.

McGlothlin and West from the USA in 1968 [85] presented a new syndrome to the world, in which they attributed to the effect of chronic cannabis intoxication by frequent and long-standing smoking. It is also known as the chronic cannabis syndrome. This is characterized by cognitive challenges, a persistent attitude of indifference, and behavior that seeks out pursuits with less reasoning and focus, leading to poor performance, and lesser academic and professional accomplishments [86]. According to Trape *et al.* [17], the majority of patients being treated for

cocaine-induced psychosis had a history of marijuana use that started in adolescence. The authors observed that cocaine consumers in Martinique, who start smoking marijuana at a young age, are highly prone to this psychotic state.

There is a report in the literature about a study that was done on a single community [67], in which marijuana usage was chronic, intense, and early because it is a natural habit for the lifestyle that has been embraced. The use of any other substance, including alcoholic beverages, was forbidden in this group. The authors came to the conclusion that the chronic and early use of this drug is significantly associated with psychotic symptoms and cognitive deficits based on comparisons with the control group, which was made up of people from the same location who did not use CS, alcohol, or drugs but who shared similar beliefs and lifestyles.

The use of marijuana has been identified as an important environmental risk factor linked to the development of schizophrenia in predisposed people [48,87-89]. Depending on the dose and age of first use, cannabis appears to double the risk of developing psychosis in vulnerable people [89].

Various studies and the experience of many professionals who accompany marijuana addicts have suggested that most disorders caused by this drug are not significantly reversed with the suspension of its use, but its continuity aggravates the disorder, leading to increasingly serious and extensive damage [82,91].

### Cannabis and Memory Deficits

THC impairs memory in its many forms. In the literature, there are reports of deficits in short-term memory, working memory, and spatial and non-spatial memory [6,45,90,91]. Such type of effect was also observed in rats and monkeys [24]. Memory deficit occurs due to the drug action on CB1 receptors in specific areas of the brain, and this action can result in alterations at the gene level, and changes in synaptic transmission and neuronal plasticity [24,27].

CB1 receptors modulate the performance of memory function through intra- and extra-cellular mechanisms. Morphological studies relate mnemonic damage to changes in brain areas associated to this function, including frontal cortex, medial temporal lobe, entorhinal cortex, dentate gyrus, and hippocampus [14,27,45,76]. Working memory processing, for example, involves the natural modulation of CB1 receptors present in the dorsolateral prefrontal cortex [61].

Cuttler *et al.* [92] openly contest those who justify the use of marijuana to deal with stress, as their work has shown that this drug exacerbates any memory impairment caused by acute stress.

The comparison between a group of 19 adolescent (15–19 years) marijuana users and a group of 21 non-users showed impairment in semantic memory (deficit in verbal learning) and working memory in users. There was an influence of age on the severity of the observed deficits [89]. The slowdown in information processing and executive function discovered in a group of early users of this drug was still present in tests

performed 3 years later [74]. Damage in the prefrontal cortex, hippocampus, and subcortical areas may be the cause of these findings.

Animal experiments confirm that THC is the main component of CS involved in memory and attention deficits. In adolescent rats treated with this cannabinoid from the 35<sup>th</sup> to the 45<sup>th</sup> postnatal day, memory tests performed on the 75<sup>th</sup> day of life (adult stage) showed a clear deficit in spatial working memory, compared to the control [27].

In addition to THC, other cannabinoids can induce memory deficits, and even more severe ones. An example is the synthetic cannabinoid WIN 55.212-2, which acts on CB1 receptors with a potent analgesic effect [45]. A single treatment on rats with this cannabinoid was potent in interrupting recognition memory, even at low doses (0.10–0.50 mg/kg) [91].

Investigations about the action of CS components on cannabinoid receptors have contributed in expanding the knowledge of neurophysiology with valuable information about the mechanisms involved in certain brain functions. An example is the suggestion by Meng *et al.* [59], based on their histological analysis of rat brains. According to them, CB1 receptors located in GABAergic interneurons of the hippocampus and retrohippocampal areas may play a role in the preparation of information for the examination and adaptation of these to the tasks being processed.

### Effects on Genital Tract and Sexual Function

Another very important but less commented fact is that the chronic use of marijuana interferes with genital and sexual functions. In a group of women in the luteal phase of the menstrual cycle, who smoked a single 1 g marijuana cigarette (containing 1.8% THC), plasma levels of luteinizing hormone (LH) dropped by 30% relative to the levels of this hormone women who did not smoke marijuana [92]. A pituitary gonadotropin is responsible for this phase of the female cycle and promotes ovulation and progesterone secretion by luteal cells [58]. In addition, marijuana can also cause galactorrhea, among other genital dysfunctions.

The use of marijuana also decreases the plasmatic concentration of LH in males [93]. This hormone activates Leydig cells in the seminiferous channels, stimulating testosterone release [58]. Although the effects of the drug are credited with improving some aspects of the subjective experience of sexual activity, there is evidence that suggests that marijuana may, in a dose-dependent manner, contribute to erectile dysfunction by activating receptors in the cavernous tissue that are antagonistic to penile erection [94,95].

Even at minimal dosages, the CS extract (intraperitoneal route) was able to drastically diminish sperm motility and count in albino mice and rats, in addition to lowering serum levels of LH and testosterone [96]. This may also be followed by a reduction in the profiles of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase [98], as well as a narrowing of the tubular diameter and injury to the seminiferous

epithelium [4,97]. Thus, CS exhibits both gonadotoxic and spermatotoxic action by increasing oxidative stress responses and causing apoptosis in testicular tissue.

The National Patient Registry, Cancer Registry, and Cause of Death Registry from Sweden were used by Callaghan *et al.* [99] to verify the potential connection between cannabis and cancer. A total of 45,250 records of young males between the ages of 18 and 21, who participated in the Swedish military recruitment evaluation in 1969–1970 and answered questions about drug usage made up the sample. One hundred and nineteen incidences of testicular cancer were identified in those who used marijuana “heavily” (defined as more than 50 times over the course of a lifetime) between 1970 and 2011. Cancer incidence was directly linked to drug use.

The use of a meta-analysis to a thorough evaluation of articles from 1980 to 2015 and from 2017 to 2019 also revealed a high correlation between frequent and chronic marijuana use and the development of testicular germ cell cancers [97-100]. Thus, it is possible to comprehend how frequent and ongoing marijuana usage might harm the natural antioxidant capacity of testicular tissue, seriously harm the male reproductive system, and cause sexual dysfunctions like impotence, infertility, and changed libido. Regarding the female sex, reports of reproductive function impairment have been made, however, there is a lack of evidence regarding physical changes to the genital organs.

### Cannabis sativa, Pregnancy, and Lactation

Among illicit drugs, marijuana has been pointed as the most used, with a prevalence of 3–30% in various populations. This is of immeasurable gravity, as THC and its metabolites cross the placental barrier [3,101]; and the problem extends beyond pregnancy, since this cannabinoid is secreted in breast milk [102]. Due to trophoblastic gene alterations that reduce GLUT1 transporters and glucocorticoid receptors, THC compromises fetal growth and neurological development, causing adverse peri- and post-natal effects. Stillbirths and premature birth are frequent with the use of marijuana during pregnancy [62,101].

Longitudinal studies on children and adolescents who were exposed to marijuana during pregnancy reveal hyperactivity as well as cognitive and behavioral problems. Studies on rats have demonstrated that THC and cannabis extract have the ability to cause neurochemical changes similar to those seen in human brain injury. In addition to changes in dopaminergic receptors, tests on the offspring of pregnant rats treated with THC during the peripubertal and adult phases revealed reduction of cerebral tyrosine hydroxylase activity in catecholaminergic neurons [103]. In midbrain neurons of rat fetuses exposed daily to cannabinoids, the activity of the enzyme tyrosine hydroxylase doubled compared to the control [103].

### Effects on the Respiratory System

Inhaled THC is rapidly transferred to the lungs, where it exerts a strong dilating effect; but, paradoxically, bronchospasm can be

the respiratory response in asthmatic individuals [15]. Regular inhalation of marijuana smoke has been associated with the risk of asthma, chronic bronchitis, and pulmonary emphysema, regardless of tobacco use [103,104]. Frequent marijuana smoking is associated to injuries and damage to the airway inflammation, leading to pneumothorax [105], and compromise airway defense mechanism [106]. According to Ribeiro and Ind [107], “bullous lung disease associated with marijuana use has been observed for a long time in clinical practice.”

Both marijuana and tobacco smoke suppress antiviral pathways, potentiate pro-inflammatory mediators, and induce oxidative stress gene expression, impairing airway epithelial cell barrier function [63]. As mentioned above, THC acts at the level of expression of the CFTR protein in the membrane of epithelial cells and, therefore, it may interfere with the regulation of hydrosaline exchange in the respiratory mucosa [64], reducing its degree of hydration. The subsequent increase in mucus viscosity compromises mucociliary clearance, as it increases resistance to cilia movement.

To complicate matters further, the tar rate in marijuana smoke is almost 4 times higher than in tobacco smoke. In addition, three marijuana cigarettes a day is equivalent to twenty tobacco cigarettes, with respect to bronchoalveolar response. Frequent breathing problems in tobacco cigarette smokers (coughing and decreased physical capacity) are common in users of more than 3 marijuana cigarettes per day. Considering that this smoke involves more intense “puffs” and no filter, one can imagine how marijuana smoke becomes more toxic to the airways, besides containing about 50% more carcinogenic substances [104,105].

Macrophages are the predominant cells (>90%) in the bronchoalveolar fluid of all individuals, smokers or not, but the number of neutrophils in the fluid is higher in smokers than in non-smokers. In heavy smoking (>10 packs/year), there is usually a higher cell density in the bronchoalveolar fluid than in light smoking (<10 packs/year), and in users of both marijuana and tobacco, this density is usually higher than in users of only one of these types of smoke [106].

### Effects on Cardiovascular Functions

Marijuana has a paradoxical effect on the cardiovascular system, because THC (and other components) acts on blood vessels, relaxing them and lowering blood pressure [15]. However, THC also acts on the adrenal medulla and releases adrenaline, and increases heart rate and cardiac output, eventually raising the blood pressure. THC has dose-dependent vascular effects. Low doses result in an increase in pressure, while high doses result in vasodilation and a decrease in pressure. However, with continued usage, this last effect progressively wanes and is replaced by a rise in blood pressure. Marijuana can also trigger cardiac arrhythmia and even atrial fibrillation. These combined events adrenaline, increased heart rate and vasodilation, sacrifice the heart, and can generate ischemic conditions in predisposed people. There

is suggestion that the risk of heart attack in marijuana users is almost 5 times greater in the 1<sup>st</sup> h of consumption [60].

Contributing to the view that marijuana smoking can compromise cardiovascular function, Lisano *et al.* [108] classified 30 participants in a study, who were physically active and users of this drug, as a moderate risk group for cardiovascular disease, due to the high mean CRP index (C-reactive protein) in relation to the control group (15 non-users).

### Eye and Visual Effects

The ocular hyperemia caused by the use of cannabis is visible, evidencing the irritative reaction that promotes reactive tearing. In 1986, McDonald and Green [49] had already shown that this manifestation would be related to an inflammatory response in the ciliary processes, due to the drug’s primary action on the vascularization of the eye. It is already known that marijuana also influences human visuomotor ability.

Acute and residual subjective physiological measurements and cognitive performance measurements were carried out in subjects who smoked a marijuana cigarette containing 0%, 1.8%, or 3.6% THC on three separate days. Assessments were made before and after smoking: On the same day and the following morning. An increase in heart rate and a reduction in pupillary reflex after smoking were present in all subjects, in addition to sharp decreases in chase eye tracking, but these changes do not observed the following day [53].

In 2002, the specific deficit in visual scanning dynamics was studied by Huestegge *et al.* [76], in marijuana users between 14 and 16 years of age. These teenage had to identify targets in a 5 × 5 matrix of visual stimuli while their eye movements were monitored. The results showed two apparent deficits in this group. One would be in short-term visual memory and the other in visual processing. That is, these individuals had difficulty organizing and ordering visual information, to facilitate data processing and select what was requested in the tests.

In another study, the group by Huestegge [109] verified the oculomotor performance in long-term marijuana users, analyzing saccadic movements and spatial and temporal parameters during reading. When compared to control, users had impaired visuospatial working memory, deficits in the temporal processing of saccadic movements and low efficiency in eye behavior in reading. In addition, the time for visual fixation and exposure of words was longer and the reinspection of excerpts in the text was more frequent.

The works by Huestegge and collaborators [76,109] clearly evidenced the oculomotor damage caused by CS in the investigation and image fixation work, and in the performance of visual memory.

### FINAL CONSIDERATIONS

Many results from scientific studies clearly show that the chronic marijuana use can open the door to psychiatric, neurological,

cardiac, respiratory, and other illnesses. Cognitive and memory deficits are among the damages resulting from prolonged use of this drug, especially when starting in adolescence. At the brain level, one of the serious effects of marijuana is the reduction in the density of dendritic branches in neurons. Another effect is on the gene expression of neuromodulators and enzymes, as in the case of tyrosine hydroxylase. Such dendritic alteration represents a decrease in the neuronal surface suitable for synaptic contacts, less neuronal connectivity, and simpler neuronal circuits, that is, functional impoverishment.

Marijuana might be regarded as “the most perverse drug” of all currently used illegal substances since it deceives users with its seemingly harmless smoke and calming and anxiolytic effects. However, in addition to other harmful consequences in cigarettes, marijuana also has the potential to be damaging to the airways. Similar to this case, marijuana compromises the protective airway barrier, amplifies pro-inflammatory mediators, promotes the expression of oxidative stress genes, and lowers the profiles of antioxidant enzymes.

Anxiety and panic attacks can be part of the life of the chronic marijuana user. Most of those who manage to overcome the risk of developing a psychotic condition (schizophrenia, mania, etc.) at the beginning of use, later on, develop some anxiety disorder and/or depression. Depression can become severe with continued use of the drug, and may culminate in suicide attempt or death. In young people with behavioral deviations or neurocognitive deficits, SC can exacerbate the preexisting problem, bringing harmful consequences to their lives.

Researches have shown that marijuana slowly deteriorates the user’s intellectual capacity, leading to poor academic performance and lower professional achievements. It is common to find a marijuana user “underemployed,” considering his/her professional degree, as he/she avoids activities that require concentration and reasoning, two functions clearly impaired by the drug.

Dependence on CS is a serious social problem and should be a concern for government and health authorities. It is a public health problem that must be included and discussed within health policies, since most of these individuals become ill and become professionally incapable in working age. Retirement is the only option after a string of sick days, which strains Social Security and the Public Health Service. There are currently authors who support the use of cannabinoids as a treatment for cancer, ataxia, psychiatric disorders, memory impairment, and other illnesses. Contrarily, numerous studies demonstrate that CS can actually exacerbate the diseases and dysfunctions that it purports to treat. In addition to *in vivo* and clinical study, considerable laboratory and *in silico* research on the pharmacological features of cannabis is needed to establish the necessary safety for their use in medical practice outside of palliative care.

The current ignorance about the possible interactions of cannabinoids with drugs or other compounds must be remembered by the physician, before recommending any treatment based on CS products. There is still no standardization in the preparation

and composition of these products; and there is a lack of consensus regarding use and therapeutic efficacy. Because the synthetic cannabinoid receptor agonist WIN 55,212-2 has been found to be more dangerous than THC itself, the road to legalizing “cannabinoid medications” is a lengthy one.

Cannabinoid treatment should not be confused with a “marijuana-based treatment,” since the regular use of this herb chronically exposes the patient to all of its components. In this case, a big risk is the THC: CBD ratio, which varies considerably even within the same plant. In fact, prescribing the use of marijuana cigarettes for some therapeutic purpose for young patients, adolescents, and children, in the absence of terminal disease, can be seen as an irresponsible act, by taking not account of the consequences of the therapy that will compromise the future of patient.

At present, any treatment with cannabinoids must be very judicious, considering the patient’s age and conditions, due to possible changes in brain metabolism and neuronal connections involved in memory and learning. In addition, there is the possibility of lasting, even definitive, changes due to the action at the gene level. Therefore, in agreement with Carranza, exposure to known and unknown risks is only justified for palliative treatments for terminal patients, elderly people or, in the case of non-elderly people, short-term treatments, similar to the use of opioids such as morphine.

## CONCLUSION

We emphasize that research carried out in the past 30 years proves the harm that the use of CS can represent for human and social health. The growing use of this drug and the call for its legalization in the country demonstrate the urgency of finding solutions to this problem, which is becoming increasingly complex.

## INDIVIDUAL CONTRIBUTIONS

Prof. C.M. Cortez idealized the study and wrote the paper. A. Cortez-Calderini conducted the literature search in the research databases. The three authors worked selecting the references in accordance to the study aim and in the final review of the manuscript.

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