Literature Review

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Bibliographic review of cannabis, cannabinoids and their health effects

Summary

Introduction: Currently the use of marijuana is very popular recreationally or therapeutically, among the different ways of consuming marijuana the most popular is by inhalation, followed by the oral route that can include the consumption of the plant, extracts and active ingredients such as tetrahydrocannabinol (THC) or cannabidiol (CBC).

Methodology and results: A systematized searching is performed in the PubMed database with the keywords *cannabis, cannabinoids, and health,* from 2016 to 2021, limited to humans, adolescents and adults, obtaining as a result 505 articles, of which 463 are eliminated, leaving a total of 42 articles to analyze.

Conclusion: In patients with diseases such as multiple sclerosis, fibromyalgia and chronic pain, who do not respond adequately to conventional therapies, it is valid to consider the use of THC or CBD to improve their symptomatology, on the other hand healthy people who use marijuana for recreational purposes are not exempt from the harmful effects that this substance can have on the body in the short, medium and long term, such as neoplasms, cardiovascular diseases, not to mention the impact it has on the body, are not exempt from the harmful effects in the short, medium and long term that this substance can have on the organism, such as neoplasms, cardiovascular diseases, without leaving aside the impact on mental health, since the consumption of marijuana favors the development of depression, suicidal ideation and suicide in adolescents.

Keywords: Cannabis, Cannabinoids, and health

Volume 14 Issue 2 - 2022

Vilchis Valentin David
Anesthesiologist of the ISSEMyM Toluca medical center, Mexico

Correspondence: Vilchis Valentin David, Anesthesiologist of the ISSEMyM Toluca medical center, Calle 3 Garantias #19 San Jeronimo Chichahualco Metepec Estado de México CP 52170, Tel 5554165470, Email dr.vilchisvalentin@gmail.com

Received: March 08, 2022 | **Published:** March 15, 2022

Introduction

Nowadays in the world the use of marijuana is very popular and is increasing both recreationally and therapeutically, nevertheless its use in medicine has long been empirical and with very few scientific evidence minimizing the adverse effects (AE) it has on health; the beneficial effects of marijuana for therapeutic purposes, have very controversial scientific evidence and for recreational use is no exception since the existing information is still insufficient.

Within the different ways of marijuana consuming, the most popular is inhalation, followed by the oral way, including the ingestion of the plant, extracts, active ingredients such as tetrahydrocannabinol (THC) or cannabidiol (CBC). This leaves a breach comparing the effects of the routes of administration, because in the inhaled form and the oral way not only the active ingredients THC and CBD are ingested, but also more compounds and at non standardized doses. It should be analyzed if the use of marijuana has harmful effects to health through consumption of the active ingredients or if they are attributed to the administration route or to the other substances consumed at the same time.

The use of a pharmacological product has always as a principle to treat a disease, nevertheless the use of marijuana has two aspects, one for recreational purposes and the other one for therapeutic purposes; on this premise it should be considered that every drug before being commercialized must be studied with principles of bioavailability, safety and its possible adverse effects, however marijuana used for recreational purposes does not have such rigorous studies. When using a drug to treat a disease, the premise of the risk-benefit of the use of one drug or any other is taken as a starting point. For this reason, patients with chronic diseases that do not respond adequately to conventional therapies evaluate the benefit of THC or CBD for the condition that is afflicting them, always considering the adverse effects that could occur during its use, nevertheless, as long as the benefit outweighs the risk, its use is valid. On the other hand, people who use marijuana for non-medical (recreational) purposes are not exempted from the short-, medium- and long-term adverse effects that such substance may have on the body, such as neoplasms, cardiovascular diseases, as well as the effect on people with susceptibility to psychiatric diseases, and it is here where the impact that the approval of the recreational use of marijuana will have on society must be analyzed.

Methodology

After systematically searching in PubMed database including clinical essays, meta-analysis, systematized reviews in English with a stablished period, from 2016 to 2021, limited to human beings, adolescents and adults with the keywords *cannabis, cannabinoids and health*; a total of 505 articles were obtained, of which 458 were eliminated for including pediatric patients, animal tests, being focused on substance abuse, talking only about the endocannabinoid system and the use of non-cannabinoid drugs. When the selected articles were read, 5 more articles were eliminated for repeating themselves or for not talking about cannabis or cannabis derivatives, which left a total of 42 articles to be included in the review (Figure 1).

Results

The uses of marijuana, and its synthetic derivatives or active ingredients is very controversial topic because of the positive or negative effects on health, as well as whether they should be legal for recreational purposes or if they have to be restricted for exclusive medical use; based on this, studies have been conducted in different people groups, both chronically ill, patients with psychiatric disorders, pregnant women, patients with acute or chronic pain and if there is an increased risk of suffering any disease associated with the use of marijuana. The National Academies of Sciences, Engineering and Medicine in a review of the literature by *Abrams Donald* found conclusive evidence that Cannabis or cannabinoids are effective

for the treatment of pain in adults, also for chemotherapy induced nausea and vomiting, spasticity associated with multiple sclerosis and is supportive in improving appetite. Evidence for Tourette's syndrome, anxiety, post-traumatic stress disorder, cancer, irritable bowel syndrome, epilepsy, neurodegenerative disorders, secondary sleep disturbances were described with limited information.[1]

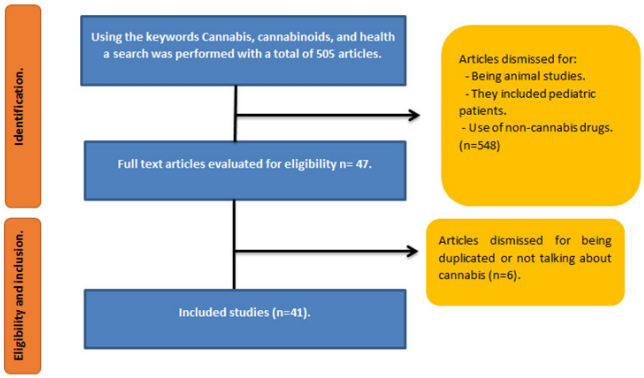

Figure 1 Systematized searching algorithm using the keywords cannabis, cannabinoids, and health.

Pain and cannabis

The management of chronic pain is a challenge all over the world, from the point of view of non-oncological pain management *Stockings Emily and collaborators* found a decrease in the intensity of pain by 30%; this percentage is the same for neuropathic pain comparing with placebo, but with no impact on physical or emotional functioning,[2] nevertheless *Fishera Emma and collaborators* mention that the quality of sleep did not improve,[3] as well as the appearance of adverse effects tends to be high up to 50%, this suggests that the number necessary to treat to benefit is high and the number necessary to treat to cause adverse effects is low.[4]

Regarding the efficacy of cannabinoids for acute pain, *Gazendam Aaron and collaborators* point out that they are favorable over placebo, while with the intramuscular route of administration there is a greater reduction of pain in relation to the oral via.[5] With respect to patients with chronic oncologic pain and comparing them with patients with chronic non-oncologic pain, *Wang Li and collaborators* obtain that medical cannabis or non-inhaled cannabinoids produce a small improvement in pain relief, physical functioning and sleep quality, accompanied by transitory adverse effects such as cognitive deterioration, vomiting, somnolence.[6]

In the review conducted by *Henshaw and collaborators* demonstrated the anti-inflammatory capacity of cannabinoids due to the fact that tumor necrosis factor alpha, interleukin (IL) -1β, IL-6 and interferon gamma, reduced their serum levels after treatment with CBD or CBD + THC, but not with THC alone, this study provides the molecular basis of why cannabinoids have positive effect in patients with chronic and acute pain.[7] Finally, it was reported that cannabis-based medications (CBM) have been shown to be effective in reducing chronic pain and although the subject remains highly controversial the primary analysis showed favorable results for CBM over placebo, despite this the clinical significance of these findings is uncertain and recent.[8]

Quality of life and cannabis

Multiple studies talk about the quality of life with the use of cannabinoids, including patients with psychiatric diseases, pain or any other condition, nevertheless the results obtained so far are not certain. Goldenberg and *colleagues* in a systematized review conclude that health-related quality of life and the use of cannabis or cannabinoids for medical conditions is inconclusive. Some patients report improvement in pain, mood, while others report reductions in health-related quality of life due to dizziness, confusion states, lethargy.[9]

Being physical activity a parameter of quality of life, there are people who claim that the use of marijuana has a positive effect on aerobic exercise, nevertheless in a review study conducted by *Zach and collaborators* concluded that there is no improvement in aerobic performance and it could precipitate angina pectoris with a lower exercise load.[10]

Mental health and cannabis (Psychiatric diseases and memory)

The effects that some substances such as alcohol or tobacco have on mental function are well known, nevertheless it is still being investigated whether there are anatomical variation that make people more prone to become addicted to a specific substance, this point does not exclude marijuana since it has been seen that the regular consumption of cannabis is associated with adverse cognitive and mental health effects, therefore *Lorenzetti and collaborators* in their systematized review demonstrated that there are alterations in brain regions involved in reward, learning and memory in regular users of cannabis or substances other than cannabis, which points to the existence of common neurobiological abnormalities that make people more susceptible to addictions.[11] *Zach et colleagues* consider that the use of cannabis for therapeutic purposes may be problematic among people with psychotic disorders, showing negative influence on cognitive assessment, particularly on short-term memory tests.[10]

It is questionable whether the psychological effects (affective and cognitive) of cannabis users differ from person to person and whether these effects are the same between users of synthetic or natural derivatives *Akram et al.* demonstrated that synthetic cannabinoids are generally full agonists at the CB1 cannabinoid receptor and therefore considerably more potent than natural cannabis and have correspondingly more severe psychological effects.[12] There are substances that when consumed can cause changes in human behavior, being important to highlight the severity of these behavioral changes, for this guy and collaborators contribute that when there is an increase in the consumption of cannabinoids should understand the form and intensity as manifested by psychotic symptoms and other psychiatric symptoms, this is based on the fact that the administration of THC significantly increases positive psychotic symptoms (delusions, hallucinations, behavioral disorganization) and negative symptoms (loss of motivation, difficulty in enjoying things) compared to placebo, and they also deny that there is an attenuating effect of the symptoms caused by THC when CBD is administered together.[13] *Alkomiet and collaborators* support the above with their review in which they argue that cannabis use is also associated with an increase in relapses, hospitalizations and severe positive symptoms in patients suffering from psychotic disorders.[14] Comparing the effects of cannabis in chronic and occasional users, *Natasha and collaborators* conclude that cannabis distorts behavior in occasional users, but not in chronic users, suggesting that there is a reduced response of the reward circuit in chronic users.[15]

The previous mentioned enables us to understand the care and risks that are taken with the use of cannabinoids, and despite the fact that a beneficial potential has been described for some psychiatric conditions; in the review carried out by *Bonaccorso and collaborators,* they address CBD and its use in substance abuse disorders, chronic psychosis and anxiety; where, despite its use, there is still limited

evidence regarding safety and efficacy, for this reason the management of these diseases with CBD should be cautious.[16] On the other hand, *Hser and collaborators* found that cannabis consumers patients living with depression or generalized anxiety disorder have shown an association between the reduction in cannabis consumption and improvement of symptoms related to anxiety, depression and sleep.[17]

Regarding a disorder such as schizophrenia, *Shweta and collaborators* emphasize that the THC component of cannabis may be the main culprit in causing psychosis and triggering outbreaks of schizophrenia in susceptible populations, and THC may also aggravate the symptoms causing a poor prognosis in patients already diagnosed; although CBD shows therapeutic effects and opposite to THC, data are minimal with limited safety and efficacy, making further research necessary.[18] Another pathology analyzed by *Orsolini and collaborators* is post-traumatic stress disorder, where they evaluate the effects of medical cannabis and synthetic cannabinoids on this pathology, reaching the conclusion that both medical cannabis and its synthetic derivatives by acting on the endocannabinoid system can have a therapeutic use to improve the symptoms of post-traumatic stress disorder, this by reducing anxiety, modulating the processes related to memory and improving sleep, nevertheless there are limitations due to the scarce evidence on safety and efficacy.[19]

Although in some pathologies cannabis and its synthetic derivatives have shown to be useful, its use is still controversial, for this reason in the review of *Botsford and collaborators* they return to generalized anxiety disorder, bipolar disorder, post-traumatic stress disorder and depression, posttraumatic stress disorder and depression, showing that the rates of problematic use of these substances are higher in these patients than in the general population, emphasizing that cannabis use is related to the onset and worsening of bipolar disorder and posttraumatic stress disorder, nevertheless, this is not clear in depression and generalized anxiety disorders.[20] Adolescents tend to abuse of substances and are more prone to have psychiatric disorders such as anxiety, depression, and suicide *Gobbi Gabriella et al.*[21] report in their meta-analysis that the relative risk for developing depression in adolescent cannabis users was 1.37 (95% CI, 1.16-1.62; I2 = 0%), for anxiety they found no significant statistic and with suicidal ideation they report an OR of 1.50 (95% CI, 1.11-2.03; I2 = 0%) while for suicide attempt it is 3.46 (95% CI, 1.53-7.84, I2 = 61.3%).

There are two conditions where cannabis has been attributed important beneficial properties, the first one is multiple sclerosis (MS) where *Amato and collaborators* mention that cannabinoids are good for the control of spasticity and pain showing good efficacy and safety.[22] In second place is fibromyalgia (FM) where *Kurlyandchik Inna*, mentions that the treatment has a pharmacological and non-pharmacological approach with ineffective results, under this premise medical cannabis has a therapeutic potential, nevertheless efficacy and safety studies are still lacking before recommending its routine use.[23] *Ashleigh and collaborators* mention that cognitive impairment is typical of schizophrenia, neurological disorders and substance abuse, which is manifested by impairment in learning, memory, attention, executive functioning, affecting daily life. This review analyzed the effect of CBD on cognitive deterioration in diseases such as schizophrenia, Alzheimer's disease, neuroinflammatory processes as well as hepatic encephalopathy or cerebral ischemia, finding that cognitive improvement in schizophrenia when using CBD has limited evidence but has shown to have a positive effect on other diseases that produce cognitive deterioration, nevertheless the mechanism by which this improvement occurs is not known.[24]

In the review conducted by *Eadie*, he reports that patients using medical cannabis compared to recreational cannabis users have different physical, emotional and physiological characteristics that modify the presentation and extent of neurocognitive dysfunction, for this reason, medical cannabis users should be advised to perform activities with cars or safety tasks, since it was shown that cognitive performance decreases when consuming THC, accentuating a few hours after administration, in addition the duration of cognitive damage is relative to each person, suggesting that there are other factors that contribute to this variability; these findings mean that THC has limitations for its use in daily life.[25] A point to consider regarding the recreational use of cannabis or its derivatives is what *Klofta et al.* describe in their review regarding the development of false memory or false memories, concluding that participants intoxicated with cannabis were more susceptible to the creation of false memories when employing an eyewitness and a virtual reality perpetrator scenario.[26]

Cardiovascular diseases and cannabis

Nowadays, one of the main causes of death worldwide are cardiovascular diseases, for this reason *Jouanjus and colleagues* examined the published evidence on the cardiovascular risk involved in the use of cannabis-based products. In this study, they emphasize that people who consume cannabis are more susceptible to suffering from acute myocardial infarction (AMI) or ischemic stroke; these effects are greater when consuming large doses of cannabis.[27] *Richards et al.* demonstrate that cannabis use raises heart rate and blood pressure immediately after use, mainly due to stimulation of the sympathetic nervous system and inhibition of the parasympathetic nervous system, precipitating cardiac arrhythmias.[28] *Rikinkumar and collaborators* in addition, with the previous idea concluding that episodic marijuana use is a significant risk factor for developing AMI, particularly in people with low cardiovascular risk.[29] Regarding patients who have presented a coronary ischemic event, *Yang et al.* found that marijuana use after AMI is associated with a greater probability of presenting an acute coronary syndrome within the first 24 hours after consumption.[30]

Pregnancy, breastfeeding and cannabis

Being a cannabis user is not limited to a certain population group, pregnant or breastfeeding women can also consume cannabis, *Roncero Carlos and colleagues* analyzed the factors associated with cannabis consumption during pregnancy, as well as the effects it has on the fetus; the results found were that not being married, low educational level and having a history of cannabis addiction, make it 2.77 times more likely that a woman continues to consume cannabis during pregnancy. Hispanic women are less likely to continue cannabis use during pregnancy compared to women of multiracial origin, the reasons for this are unclear. From the 14th week of gestation, cannabis receptors are present in the placenta and in the fetal brain, mainly in the frontal region and cerebellum, causing a slow development of these structures compared to the rest of the brain, in addition to being lipophilic, one third of what is in plasma crosses the placenta and is excreted in breast milk, this can alter the function of the cannabinoid receptor and cause changes in the dopaminergic and opioid system of the infant.[31] With cannabis use during lactation *Ordean* reports that women who use the drug during lactation put their infants at risk by exposing them to cannabis in breast milk, having a negative impact on psychomotor and neurocognitive development, thus concluding that women should abstain from cannabis use during lactation or reduce consumption to a minimum if abstinence is not possible.[32]

Infectious diseases and cannabis

Ghasemiesfe Mehrnaz and collaborators report that there is an association between cannabis consumption and latent tuberculosis,[33] which gives rise to the need to investigate the consumption of

marijuana when outbreaks occur, especially to see if there are other practices that favor the perpetuation of the infection. Taking into account the current situation of the COVID-19 pandemic, Khalsa and collaborators mention that COVID-19 has wreaked havoc on mental health, CBD has been promoted for the treatment of mental health problems and for substance abuse associated with COVID-19, nevertheless they conclude that there is still a lack of impartial clinical evidence that demonstrates that it has positive effects for treating these conditions.[34]

Effects of cannabis on inflammatory bowel disease

Cassio and collaborators describe inflammatory bowel disease as a chronic and recurrent condition, which mainly includes ulcerative colitis (UC) and Crohn's disease (CD), currently, cannabis has been used for the management of these two conditions and has been shown to improve the symptoms and quality of life of these patients; despite the evidence, it is still not possible to establish a treatment criterion since the doses, the via of administration and the active principle of the plant that is useful are not known.[35] In this same area, *NaftaliI and collaborators* investigated whether there is an association between cannabis consumption and remission of ulcerative colitis by endoscopy. In this controlled study, patients received cigarettes containing 0.5 g of cannabis with 80 mg of THC or placebo cigarettes for 8 weeks, obtaining as a result that the Lichtiger index improved in the cannabis group, concluding that in the short term treatment with THC-rich cannabis induced clinical remission and improved quality of life in patients with mild to moderate ulcerative colitis, nevertheless, these beneficial clinical effects were not associated with a significant anti-inflammatory improvement in the Mayo endoscopic score.[36]

Cancer, sexual health and cannabis

Currently there is still uncertainty about whether or not there is an increased risk of developing some type of cancer due to cannabis consumption, considering the above *Ghasemiesfe Mehrnaz and collaborators* in their literature review conclude that smoking marijuana is associated with the development of testicular germ cell tumor and non-seminoma testicular germ cell tumor, it is not clear if this association is due to the route of administration or if it is due to the active ingredients.[37] *Rajanahally et al.* take up this issue by concluding in their systematized review that marijuana exposure is an independent risk factor for testicular cancer, data on bladder cancer are contradictory while it turns out to have antineoplastic effects on prostate cancer.[38] A point that is not neglected is the effect that smoking cannabis has on oral health where *Keboa Tambe et al*. conclude that inhaling cannabis is detrimental to the health of the periodontium while the association with other oral diseases (dental caries, soft tissue lesions and oral cancer) is inconsistent, although studies suggest that smoking cannabis is an additional underlying risk factor.[39] Some association has been seen between cannabis use and testicular cancer, but the impact on hormone function or semen remains unclear, although it has been argued that cannabis may have an inhibitory role on testicular hormone function,[39] for this reason *Belladelli and collaborators* in their review where they included 4014 men with information on semen quality and 4787 men with information on testicular hormonal function, reported that 44% of all patients had modifications in seminal and hormonal parameters, concluding that the evidence does not suggest a clinical relationship between cannabis consumption and changes in testicular function.[40] When taking into account male sexual function in cannabis users it has been found that marijuana can improve the subjective experience of sexual intercourse while potentially contributing to erectile dysfunction (ED) in a dose dependent manner,[39] to this *Pizzol and collaborators* add that the overall prevalence of erectile dysfunction in cannabis users is 69.1% (95% CI: 38.0 to 89.1), while the corresponding figure in controls was 34.7% (95% CI: 20.3 to 52.7), concluding that the OR of ED in cannabis users is almost four times higher than that in non-users.[41]

Discussion

Cannabis is one of the drugs that has increased its consumption worldwide for both medicinal and recreational use, for this reason it is important to regulate treatment standards for patients and to determine the severity of the adverse effects that these could manifest. For medical use, the risk-benefit balance must be considered, while for recreational use, the potential health effects for both the individual and society must be considered.

Before using cannabis and its derivatives for medical purposes, the patient must be rigorously selected to offer benefits with the medication, especially because of the controversy regarding the safety and efficacy of the doses used to mitigate symptoms such as pain, spasticity and other symptoms without causing the patient to suffer serious adverse effects. At this point, those who could benefit from cannabis therapy or its derivatives are patients with terminal diseases such as cancer, where life expectancy is shortened by the natural history of the disease, as well as patients undergoing chemotherapy where cannabinoids have shown to have good results in mitigating nausea and vomiting induced by chemotherapy. Another pathology to consider is multiple sclerosis, in which patients who have used conventional therapies without significant improvement, cannabinoids provide an opportunity for treatment, as it is a therapy that has shown a positive effect and although adverse effects are manifested, the benefits of its use have improved the quality of life of these patients. A medical treatment should always be individualized, that is why there are patients who, when receiving cannabinoid therapy, report improvement in pain and mood, nevertheless there is a counterpart where the adverse effects can be so intense that they do not improve their quality of life.

The effects of the use of cannabinoids on psychiatric disorders such as post-traumatic stress disorder, depression, schizophrenia, anxiety and psychosis, has two sides, one of those who believe that improves the symptoms of these diseases and the other side where the current evidence shows that the use of cannabinoids especially in chronic form worsens the symptoms, this was proven by reducing the dose of cannabis consumption in patients diagnosed with depression and anxiety presenting improvement of the symptoms of these diseases; It has also been shown that cannabis consumption triggers episodes of psychosis in healthy people with certain susceptibility and in those who already knew this diagnosis present more frequent and severe episodes, as for the effects it may have on the cognitive state, it has been seen that cannabis intoxication generates states of false memory, when accompanied by false visual and verbal testimonies.

Studies analyzing the effects of cannabis at the cardiovascular level have shown that those who consume it are more susceptible to acute myocardial infarction or cerebrovascular accidents, in addition to the fact that those patients who have had an acute myocardial infarction and within 24 hours post-infarction consume cannabis, in view of this evidence, the recreational use of marijuana does not show to have any beneficial effect at the cardiovascular level, besides having a negative impact on public health, making healthy people more susceptible to suffer a cardiovascular disease. The use of cannabis is contraindicated during pregnancy and breastfeeding, since it has been seen a delay in the development of the fetal brain and to date no positive effect has been seen that can be attributed to the consumption of cannabis.

Citation: David VV. Bibliographic review of cannabis, cannabinoids and their health effects. *J Anesth Crit Care Open Access.* 2022;14(2):62–67. DOI: 10.15406/jaccoa.2022.14.00508

One of the diseases where a positive effect has been shown is in inflammatory bowel disease including CD and UC, although an improvement has not been seen in terms of endoscopic classification, it has shown to have a beneficial effect on the patient's quality of life. For infectious diseases such as tuberculosis, it has been seen that patients who tend to develop this disease have a high prevalence of cannabis use, and there is a strong association between recreational cannabis use and the risk of developing latent tuberculosis. The relation between cannabis consumption and cancer development is mainly focused on people who use it recreationally, having an important impact on public health since its consumption has been strongly associated with non-seminoma testicular cancer and despite showing a protective role in prostate cancer, its use is not justified for the entire population, the last one could be aimed at patients at high risk of prostate cancer. Another point to consider is the effect on sexual function and although it has been seen that it improves the subjective experience of sexual relations, it also increases 4 times the possibility of having ED compared to those who do not consume.

Conclusion

The use of cannabis and its derivatives for medicinal or recreational purposes remains controversial, although its consumption has adverse effects on health, certain patients may find relief from their symptoms, these patients should be chosen with great caution and have a strict monitoring for the harmful effects they may present. Given the current evidence, the recreational use of cannabis has a negative impact on public health by increasing cardiovascular risk, worsening coronary heart disease and cerebral vascular disease. It should not be overlooked that cannabis consumption has effects on the behavior of some susceptible individuals, generating episodes of psychosis, worsening anxiety disorders, depression and suicidal ideation. Finally, it should be emphasized that a problem detected with the recreational use of cannabis is that in a state of intoxication, memories of actions that the person did not perform can be created.

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Citation: David VV. Bibliographic review of cannabis, cannabinoids and their health effects. *J Anesth Crit Care Open Access.* 2022;14(2):62–67.
DOI: 10.15406/jaccoa.2022.14.00508