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Modern methods of treating marijuana addiction (cannabis use disorders) and its influence on health

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Abstract

Introduction: Worldwide, cannabis is the most widely used illegal psychoactive substance and the third most common drug, after alcohol and tobacco. Cannabis use disorder (CUD) affects approximately 10% of the 193 million cannabis users worldwide. In recent years, cannabinoids have become more and more popular. The CUD is becoming a growing social and health problem. The search for effective forms of pharmacotherapy is still ongoing,

and an effective combination of psychotherapy and pharmacotherapy may be crucial for the future of CUD treatment.

Material and method: The article was based on a review and analysis of publications and discoveries in recent years, which were available in the PubMed and Google Scholar database.

Results: 82 study participants attempted abstinence from cannabis use. In the final primary endpoint analysis, both 400 mg of CBD and 800 mg of CBD were more effective than placebo in reducing cannabis use. 50 people who were addicted to cannabis treated with gabapentin showed a significant reduction in cannabis use and cannabis withdrawal compared to placebo. Moreover, 70 men addicted to cannabis were randomized and those, who used FAAH inhibitors reported fewer cannabis withdrawal symptoms, less cannabis use and lower THC urine levels than placebo users.

Conclusions: Gabapentin has been proven to show a reduction in CUD. The use of CBD, FAAH inhibitors and psychotherapy MET/CBT/CM also appear to be effective. In addition, the use of the principles of People-First Language, avoiding slang and idioms, using medical and curing vocabulary, respects the addicted person, and also positively influences the chances of abstinence.

Keywords: cannabis; CBD; CUD; psychotherapy; pharmacotherapy

Introduction

Cannabis is a group of plants originating from Asia with a psychoactive effect. Cannabis is the most popular type of hemp sativa , and the term Cannabis describes the psychoactive substances contained in it, i.e. cannabinoids . Hemp owes its narcotic effect to the content of over 100 different cannabinoids . Among these substances, the compounds Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been the most studied. THC is responsible for the main effects of cannabis, connecting to the CB1 receptors in the brain and creating a euphoric state. [1,2,3,4] In addition, cannabis is the most widely used, cultivated and trafficked illicit substance in the world, and the third most commonly used drug after alcohol and tobacco[1,5]. The method of use is inhalation of cannabis smoke (from cigarettes, water pipes). The effect achieved is described as a relaxing and pleasant sensation that lasts for about 2-3 hours. Cannabis can also be consumed orally. Then the onset of action is slower, peaks after 2-3 hours and lasts longer (4-12 hours). The intensity of the effects varies with THC dose, frequency of use, predisposition to mental illness, and personality traits. The effects of cannabis include a state of euphoria, laughter, calming, changes in time perception, increased sensitivity to external stimuli and memory gaps. Increased appetite and dry mouth are often felt after taking it. Side effects include panic attacks, dysphoria, psychotic episodes, anxiety and paranoia. High doses of THC can result in more frequent and serious side effects from acute intoxication, which often leads to emergency room visits and hospitalizations[3]. In surveys, people who report using cannabis extracts report more symptoms of addiction and psychological stress than marijuana users[2]. Heavy cannabis use has long-term adverse effects on short-term memory, attention, coordination, and reaction time.[3] Non-medical use of cannabis is illegal in most countries, although by 2019, 12 US states, Uruguay and Canada had legalized adult recreational use of cannabis. [2] People who use marijuana (hemp) may mistakenly believe that it does not cause dependence syndrome or withdrawal symptoms. However, regular cannabis use and its effects on the endocannabinoid system (ECS) have been proven to lead to CUD (*cannabis use disorders*). Despite the lenient public perception of marijuana, cannabis use disorder (MID) is a major public health problem [6]. It is estimated that CUD occurs in about 10% of users worldwide and in up to a third of daily users. Treatment of CUD is often complicated by co-occurring mental health disorders and other addictions[2,7]. Moreover, addicts interested in quitting addiction are often left to their own devices because of the lack of adequate support services. [5]

CUD

CUD is addiction defined as the inability to stop using cannabis , despite causing physical and psychological harm. [2] Factors such as genetic susceptibility, early life trauma, mental health problems, tobacco use, high-potency marijuana, early onset, and heavy use play an important role in the development and severity of CUD. [4] According to DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*), a diagnosis of CUD requires the presence of at least two of the following symptoms for a 12-month period, with 4–5 symptoms representing moderate use disorder and 6 or more symptoms meeting criteria for severe CUD.

1. Using cannabis more often and in larger amounts than intended
2. Inability to reduce or control the amount of marijuana used, despite repeated attempts
3. The time taken to buy cannabis , use it, and get back to normal takes up a large part of your life.

4. Feeling a strong urge to use cannabis .
5. Repeated failure to fulfill obligations at work, study or home
6. Continuing to use cannabis despite repeated negative effects on relationships
7. Giving up on a range of important activities (e.g. social, work or leisure) as a result of cannabis use
8. Using cannabis in a way that puts the person at risk of harm
9. Continuing to use cannabis despite physical or mental health problems
10. Having to use more cannabis to get the same effect, or experiencing lesser effects with the same dose
11. Withdrawal symptoms after stopping use[2,3]

Cannabis withdrawal symptoms begin within the first 24–48 hours of abstinence, peak in the first week, and may persist for up to 1 month after last use[2,5]. According to the DSM, at least three of the following symptoms must occur within 1 week of cessation cannabis use: irritability, anger or aggression; nervousness or anxiety; difficulty sleeping (such as insomnia or disturbing dreams); decreased appetite or weight loss; anxiety; depressed mood; and at least one physical symptom causing severe discomfort such as abdominal pain, tremors, sweats, fever, chills, or headache[2,3]. Statistically, cannabis use before age 16 predisposes to the development of CUD, other SUD *(substances use disorder*), an anxiety disorder, increases the risk of car accidents, antisocial behavior, and early school leaving compared to non-users or those who start using cannabis later in life. [2]

Epidemiology

Due to the smaller impact of marijuana on the health and environment of users than other drugs, the problem of addicted people remains unnoticed in many countries. In addition, patients with CUD feel the need for treatment less often than those with other SUD, and even when they feel the need, they often do not make the effort to start treatment or face practical difficulties in accessing therapy. It is estimated that around the world, 192 million people use cannabis (according to WHO (*World Health Organization*) 2.5% of the population), and about 22.1 million people suffer from CUD, two-thirds of whom are men. Of the community of regular cannabis smokers, 8% to 12% develop moderate to severe CUD. The difficulty of treating CUD is that 75% of addicts also have another SUD and comorbid mental illnesses - 26.6% of people with schizophrenia meet the criteria for CUD. [1,2,4,5,7,8] On average, the first use of cannabis occurs in late adolescence, and the median incidence of CUD is 18-19 years. [2] Note the growing problem of cannabis abuse by veterans in the US. About 9% of them use cannabis and 1% have been diagnosed with CUD. [8,9] In a study on people using marijuana (n = 11,272), the probability of developing CUD was examined, which was as much as 27%. Men with an early onset of use and belonging to an ethnic minority are more likely to use it. Risk factors include: genetics (51-59%), difficulties in contacts with peers, anti-social behavior, moving out of home, giving up education, acts of violence, impulsiveness, social problems and negative life situations. [2.10]

Mechanism

THC's main action is by binding to the CB1 receptor (present in the brain), modulating brain function. The endogenous cannabinoid system (ECS), which includes CB1 receptors, plays a role in maintaining homeostasis - it is involved in nutrition, sleep, emotion regulation and stress response modulation, which is why using cannabis produces sedation and other effects. In addicts, a deficiency in CB1 activation can cause cannabis withdrawal symptoms such as anorexia, sleep disturbances, and negative mood. THC-CB1 receptor binding activates G proteins and inhibits adenylyl cyclase activity. THC indirectly increases dopaminergic activity, i.e. it increases dopamine secretion, like many other stimulants, which affects the reward system in the brain. At the molecular level, heavy and chronic cannabis use is associated with dysregulation ECS, causing down-regulation of CB1 receptors and lowering the level of FAAH (ang. *fatty acid amide hydrolase*) in the brain. Studies have shown that CB1 receptor density normalizes by 4 weeks after cannabis withdrawal, indicating that the effects of chronic cannabis use are somewhat reversible. We see reduced dopaminergic function in chronic cannabis users, and PET studies have shown a decreased ability to synthesize dopamine in such cannabis users, which explains the reduced response to the rewarding effect of cannabis and reduced motivation.[2,3,5,11]

Consequences

Too much cannabis use can lead to poisoning. Poisoning is characterized by various symptoms such as extreme agitation, dysphoria, delusions, hallucinations, convulsions and even suicidal thoughts. [3] Nausea, vomiting may occur, and the picture of poisoning may be similar to delirium tremens , therefore it is important to determine the substance taken. The classic symptoms of CUD include episodic or chronic mood swings, anxiety, and thought disorders. Differential diagnosis requires information on the regularity of cannabis use and the exclusion of

cannabis-induced psychiatric disorders. Cannabis-induced psychosis is one of the more difficult differential diagnoses because patients with primary psychotic disorders often use cannabis. Recurrent vomiting may be a symptom of cannabis hyperemesis syndrome (CHS), which has been reported in emergency department patients with cyclical vomiting and a history of cannabis use.[2] Studies show that long-term use of cannabis impairs cognitive functions, episodic memory, short-term memory, long-term memory and attention, with these effects reversing after adequate abstinence, [2,4,6]. People with CUD often report problems with school, work, family, financial and emotional, which may indicate the negative impact of addiction on all aspects of life. [7] CUD increases the predisposition to mental disorders five times. Studies have noted that 24% of subjects with bipolar affective disorder use cannabis, 20% have CUD, and that in people with CUD, the prevalence of generalized anxiety disorder is 8.9%, social anxiety disorder 8.4%, panic disorder 7.7% and specific phobia. The most serious and unpredictable negative effects are especially affecting younger, naive users who abuse synthetic cannabinoids . [2,3,12] Some studies suggest that heavy use of cannabis may cause a decrease in IQ, although new research more closely associates the decrease in intelligence with the effects of cannabis intoxication or low socioeconomic status. [4] Long-term cannabis abuse can affect the cardiovascular, gastrointestinal, immune, neuromuscular, ocular, and reproductive systems, but the main adverse effects of cannabis smoking are on the respiratory system and the incidence of bronchitis. [2.13]

Pharmacotherapy

20 years of research in laboratories and clinical tests have resulted in the demonstration of drugs effective in treating cannabis withdrawal and reducing its use.[5] Nevertheless, so far no substances for the pharmacotherapy of CUD have been approved by the FDA, although some drugs have been proposed for off-label use. Preferred pharmacological agents are the ones that improve the condition of patients and alleviate the effects of cannabis withdrawal. Different ways of using cannabis (smoking, vaping, eating) as well as the noticeable trend of increasing THC concentration in products may affect the pharmacokinetics and pharmacodynamics of THC. In order to increase effectiveness, strategies of combined, synergistic therapies should be sought. Given the success of conceptually similar treatments for SUD, agonist therapy is also being considered in the treatment of CUD.[2,5,9]

CBD

CBD, or cannabidiol , is one of the many cannabinoids found in cannabis. It has a wide range of pharmacological actions, affecting many classes of receptors and enzymes, therefore interactions with other drugs should be monitored, as cytochrome P450 enzymes may be inhibited by CBD. Although CBD is similar to THC, it binds weakly to the CB1 and CB2 receptors, while in the ECS it acts as a negative allosteric modulator of the CB1 receptor, and also inhibits the reuptake and hydrolysis of endocannabinoids . It has potential as a safe, effective and well-tolerated replacement for THC to reduce cannabis use. Study participants meeting the DSM-5 criteria took part in a 4-week treatment with oral CBD at a dose of 200 mg, 400 mg, 800 mg or placebo. In addition, all participants underwent a motivational interview. The study showed that the 400mg and 800mg doses were more effective than placebo. Another 10-week open-label study found that administration of CBD was associated with improved mental well-being and cognitive function in regular cannabis users. Treatment with CBD offers hope, but the limitations of the study include short treatment period and insufficient sample size to properly estimate effect size. More evidence and research are needed [11,12]

Gabapentin

Gabapentin is a GABAergic drug that acts by blocking the 2d alpha subunit of voltage-gated calcium channels at selective presynaptic sites. It is approved for the treatment of epilepsy and neuropathic pain. Clinical evidence has shown that gabapentin reduces appetite, reduces sleep and mood disorders during alcohol withdrawal, and improves cognitive performance. The anxiolytic effect of gabapentin has been proven , which can be used in the treatment of bipolar disorder and addiction. Patients receiving gabapentin (N=50) significantly reduced their cannabis use compared to those maintaining placebo. In addition, gabapentin was associated with a reduction in depressive symptoms and better neurocognitive outcomes . Gabapentin also worked better than placebo for cannabis withdrawal symptoms, including cravings and problems secondary to marijuana use. [5,7,9]

Mirtazapine

Mirtazapine is a drug that increases noradrenergic and serotonergic transmission by blocking the presynaptic inhibitory autoreceptor alpha 2. This causes sedation and increases appetite, which is why it is used as an antidepressant. Insomnia and decreased appetite are problematic cannabis withdrawal symptoms. Studies have shown that mirtazapine improves appetite and positively affects sleep, reducing withdrawal symptoms in CUD. However, it has no effect on relapse prevention and other symptoms of cannabis withdrawal, such as depressed mood. While mirtazapine is potentially useful in the treatment of insomnia and appetite control during cannabis withdrawal, it is probably not sufficient as monotherapy for CUD. It can be considered in combination therapy with other drugs that complement the treatment. Unfortunately, mirtazapine can cause severe side effects, especially gastrointestinal, and/or exacerbate cannabis use. [5]

Cannabinoid agonists

Cannabinoid agonists as withdrawal or maintenance treatment are the most studied, as a similar approach has worked well for other SUDs. Three cannabinoid formulations were tested: two pharmaceutical cannabinoids (nabilone and dronabinol) and a cannabinoid extract (containing a 1:1 ratio of THC to cannabidiol) known as nabiximol. [3]

Nabilon

In a laboratory study (n=11), nabilone was able to reduce cannabis withdrawal symptoms when dosed once daily, and also prevented relapse in a laboratory model while showing a low risk of abuse. Another laboratory study showed that the combination of nabilone and zolpidem can improve outcomes in the treatment of cannabis abuse. Research suggests that nabilone may show promise in the clinical setting of CUD, although previous research has been limited to laboratory settings only.[3]

Dronabinol

Dronabinol is a THC formulation that has been approved by the FDA for the prevention of chemotherapy-induced nausea, vomiting, appetite stimulation, and weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS). It is a direct CB1 agonist, so there is a solid theoretical basis for its usefulness in the treatment of CUD, which is why many studies have been conducted with its participation. It has shown promising results, reducing withdrawal symptoms, limiting the effects of smoking cannabis, and reducing cannabis use. At a dose of 10 mg five times a day in laboratory studies, it reduced cannabis cravings and withdrawal symptoms without causing intoxication. A greater reduction in withdrawal symptoms was noted at the 90 mg/day dose, but some signs of cannabis-like intoxication were associated with the higher dose. In a large randomized controlled trial (n=156) in which cannabis-dependent adults received either dronabinol 40 mg/day or a placebo for 12 weeks with concomitant psychosocial treatment, both treatment groups reported a reduction in cannabis use . Dronabinol was shown to improve retention and reduce symptoms withdrawal but has no effect on abstinence. Negative results were also seen in a large trial of co-administration of dronabinol 60 mg/day and lofexidine 1.8 mg/ day . No differences in treatment were noted for abstinence, withdrawal symptoms, or maintenance. On the other hand, a recent study comparing 12-day use of high-dose dronabinol 180-240 mg/day, 120 mg/day dronabinol, and a placebo showed a reduction in cannabis use in both cases. These results suggest that higher doses of dronabinol may be needed . [3,7,11]

Nabiximols

More promising results have been obtained with nabiximols , which combine THC and CBD. A stationary clinical trial showed a positive effect in reducing withdrawal symptoms, although abstinence rates did not differ from the placebo group. Two published studies have investigated nabiximol. An abstinence study in inpatients (n = 51) showed that nabiximols reduced cannabis withdrawal symptoms and cravings, but no reduction in cannabis use was seen in study participants during follow-up. A later outpatient study (n = 40) tested the effect of using nabiximols for 12 weeks in combination with motivation-enhancing therapy (MET). There is no difference in abstinence between nabiximol and placebo. [3.7]

FAAH inhibitors

FAAH inhibitors increase the level of the endocannabinoid AEA (N- arachidonoylethanolamine), which causes anxiolytic and antidepressant effects. FAAH inhibitors, like CB1 agonists, have been shown to alleviate cannabis withdrawal symptoms in mice, but differ from these drugs in the lack of apparent vulnerability to abuse. A study was conducted (n = 70) in men addicted to cannabis. The study included 5 days of initial inpatient treatment and the remaining 4 weeks with drugs delivered in an outpatient setting. Those randomized to FAAH inhibitors reported fewer cannabis withdrawal symptoms and reported statistically significantly less cannabis use throughout the study and significantly lower THC urine levels than those who received placebo. Although the results are promising, further studies are needed to test the effectiveness of FAAH inhibitors in the treatment of CUD. [3,7,14]

Ketamine

Ketamine is an NMDA receptor antagonist used for anesthesia. Eight cannabis addicts receiving MET and behavioral therapies completed a 6-week, single-blind, outpatient study. During the course of the study, participants received one or two infusions of ketamine . Ketamine infusions were well tolerated and no adverse events occurred. The final results indicate that the frequency of cannabis use decreases significantly in those taking ketamine . Future research will be crucial to determine the effectiveness of ketamine and better understand the interaction of ketamine infusions with behavioral treatment. [15]

Varenicline

Varenicline is a drug used to treat nicotine addiction. Its use in the treatment of CUD has been proven. Participants in a 6-week randomized, placebo-controlled pilot study received either varenicline (n = 35) or placebo (n = 37) and short-term motivational therapy. Varenicline users had higher patient-reported abstinence rates at the final study visit. The results confirm the possibility of using varenicline as a candidate for CUD pharmacotherapy, but it is crucial to conduct a larger-scale efficacy study. [16]

Psychotherapy

So far, no drugs have been approved by the FDA for the treatment of CUD, which is why psychotherapy is the first-line treatment for adolescents and adults. There are many types of psychosocial approaches, including Cognitive Behavioral Therapy (CBT), Motivation Therapy (MET), Crisis Intervention (CM), Social Support Counselling, Drug Education Counselling, Relapse Prevention, Mindfulness Meditation and Mutual Aid Groups. Each approach seems to add something unique. MET is effective in engaging ambivalent individuals, CM leads to longer periods of continuous abstinence during treatment, and CBT works to increase periods of abstinence after treatment. Unfortunately, too few studies of CUD treatment using social support counseling, drug education counseling, relapse prevention, mindfulness meditation, and mutual aid groups have been conducted to determine effectiveness. Better effects have been seen by combining approaches and extending the duration of therapy. In the treatment of adults, the combination of MET/CBT/CM is most effective in reducing the frequency and amount of use, with limited impact on maintaining abstinence. Those taking MET/CBT showed a reduction in cannabis use for up to 34 months. [2,5,7,17,18] Effective psychosocial approaches for adolescents with CUD include multidimensional family therapy (MDFT), functional family therapy, MET, CBT, and crisis intervention integrated with MET and CBT. MDFT involves at least one caregiver and focuses on four aspects of treatment - adolescent, parental, interactive and non-familial. A randomized trial comparing MDFT with CBT in 224 substance abuse adolescents was performed.

MET

It consists of about 4 meetings of 45-90 minutes, in which the therapist strives to increase the patient's motivation for abstinence. The therapist shows empathy, respect and a non-judgmental perspective. It encourages to give up the addiction, presenting the advantages and disadvantages of the change, and helps the patient to identify what is undesirable, toxic and unhealthy in his life. In the later stages, this is to help the patient recognize risk factors and increase self-efficacy. [2,7,17]

CBT

CBT assumes that those who relapse do not have the skills to deal with the factors that trigger drug use. It is an approach focused on teaching the patient to cope with abstinence, stressors, high-risk situations, learning to refuse and reduce use, and prevent relapse. Together with the therapist, the triggers for cannabis use are interpreted. The therapist conducts up to 14 counseling sessions of approximately 45-60 minutes and assigns exercises to the patient for the time between sessions. Thanks to homework, the patient's skills are consolidated, and the patient's sense of effectiveness and faith in the possibility of change is increased. Participants in the study (212 people) significantly reduced the frequency of marijuana use and reported fewer marijuana-related problems thanks to CBT. While two-thirds of all participants achieved initial abstinence after treatment, only 14% maintained it after one year of follow-up. [2,7,17,19]

CM

Crisis Intervention (CM) is a counseling approach that uses the principles of reinforcement and in some cases punishment to achieve and maintain abstinence by attending therapy sessions and providing a "clean" urine sample. Rewards such as money or vouchers are used to increase efficiency and improve treatment outcomes. CM strategies that reward are more effective than those that punish. CM procedures have been shown to be effective, particularly in reducing substance use in the short term. [2,7,19]

Communication

An important aspect of cooperation with a person with CUD is proper communication. Attention should be paid to the language used when talking to an addict so that the conversation motivates the patient to endure abstinence. Language marginalizes, depersonalizes, and stigmatizes addicts, so the therapist should be careful with terms like "drug" and "habit" as they perpetuate the stigmatizing belief that addiction is a failure of morality, personality, or willpower. Slang and idioms (clean/dirty) should be avoided and instead more attention should be focused on using medical and healing vocabulary such as "substance use disorder". The terms "substance use disorder" and "addictive disease" define addiction as a health problem. In addition, it is worth using the PFL (*People First Language*) principles, which consist in placing the individual in the first place before words describing his condition, e.g. "person with cannabis use disorder". This is intended to reinforce the identity of the person with substance abuse problems and to emphasize that addiction does not predefine the whole character.[20]

Conclusions

CUD is becoming a growing problem around the world. Psychotherapy is not enough to maintain abstinence, so therapies combined with medication are needed to increase the effectiveness of treatment. Currently, the combination of MET/CBT/CM is the most effective method of psychotherapy for patients with CUD. The most promising at the moment seem to be CBD, gabapentin and FAAH inhibitors, although large-scale studies with greater reliability are lacking. The agonist approach in pharmacotherapy has been found to be less effective in CUD than in other addiction therapies. In a conversation with an addicted patient, one should follow the rules of communication that do not stigmatize, but support.

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