Cannabis Use and Disorder: Epidemiology, Comorbidity, Health Consequences and Medico-Legal Status

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Abstract

Marijuana (cannabis) is the most commonly used drug worldwide. It is a harmful drug for teenagers as it may result in the abnormal development of their developing brains. It exhibits psychoactive properties due to the presence of cannabinoid delta-9-tetrahydrocannabinol (THC), which binds to two types of endogenous G-protein-coupled cannabinoid receptors-CB1 and CB2. Regular, heavy, or daily marijuana use and younger age at first use can lead to adverse medical, mental health, psychosocial, and cognitive outcomes, possibly due to abnormal brain development. Synthetic cannabinoids can exhibit more intense and longer-lasting effects than natural cannabis and may not be detected in urine toxicology. First line therapy for cannabis use disorder is psychosocial treatment. Dronabinol and gabapentin are effective in the treatment of cannabis withdrawal symptoms.

Keywords: Marijuana; Cannabis; Drug use; Drug misuse; Substance use

Introduction

Marijuana (cannabis), the most commonly used drug worldwide, is harmful for teenagers as it may result in abnormal development of their developing brains. Its psychoactive properties are primarily due to the presence of delta-9-tetrahydrocannabinol (THC), a cannabinoid and partial agonist, which binds to CB1 and CB2, the two types of endogenous G-protein-coupled cannabinoid receptors. The paper focuses on severe cannabis disorder. In addition to outlining the epidemiology and current worldwide status of marijuana use, the current paper outlines the mechanism of action of THC and discusses the adverse effects and implications of regular, heavy, or daily marijuana use on medical, mental health, psychosocial, and cognitive outcomes.

Epidemiology

Marijuana (cannabis) is the most commonly used drug worldwide [1]. Approximately 10% of people who regularly abuse marijuana are estimated to develop cannabis use disorder. In 2016, cannabis was used by an estimated average of 192 million people (range, 166-234 million) worldwide, of which an average of approximately 3.9% (range, 3.4%-4.8%) aged 15–64 years, suggesting a 16% increase in prevalence since 2006 [2]. Marijuana is harmful for teenagers and may cause abnormal development of their developing brains [3]. Cannabis use by adults, instead of that by adolescents, has considerably increased over the past decade [4].

Some countries, such as Uruguay and Canada, have legalized marijuana [5]. At the United States federal level, cannabis products are categorized as Schedule 1, which means that they are currently assigned no accepted medical use and carry a high abuse potential [6]. To date over 30 states have either decriminalized medical marijuana or are reviewing legislation to permit the use of low-dose delta-9-tetrahydrocannabinol (THC) products for specific medical indications. As of 2018, nine states have allowed the retail sale and possession of recreational marijuana [7]. In regions where marijuana use is legal, ingested and vaporized forms are popular. However, these may pose a risk due to unintentional ingestion by children or excessive use by adolescents and adults.

Mechanism of Action

The psychoactive properties of cannabis are primarily due to the presence of the cannabinoid delta-9-tetrahydrocannabinol (THC), the concentration of which is commonly used as a measure of cannabis potency. THC binds to two types of endogenous G-protein-coupled cannabinoid receptors-CB1 and CB2 and is partial agonist of these receptors. CB1 receptors are distributed throughout the brain and the body, including the vascular endothelium, liver, and adipose tissue. CB2 receptors...
are present on immune cells throughout the body (including brain microglia) and on some neurons [8].

THC activates CB1 receptors in the dopaminergic mesolimbic brain circuit, resulting in increased presynaptic dopamine release, which in turn activates the brain reward system. This causes positive reinforcement of marijuana abuses.

Cannabis is most commonly consumed via smoking, and its smoke, similar to second-hand tobacco smoke, is toxic. The use of vaporizers or hookahs does not eliminate the toxic chemicals in marijuana smoke. Orally ingested cannabis is absorbed more slowly, with peak plasma THC concentrations observed 1-4 hours after ingestion. Thus, it is less likely to be abused [9,10].

Family, twin, and adoption studies suggest that-for both initiation of cannabis use and development of cannabis use disorder—there is a substantial degree of heritability. Genetic studies show that at least half the risk for initiating cannabis use or developing cannabis use disorder comes from environmental factors [11,12].

Although marijuana has been characterized as a “gateway drug”, there is little evidence supporting this theory. Possibly, the patients who abuse marijuana tend to associate more with people who abuse other drugs or have access to other drugs. Peer pressure is another factor influencing the abuse other drugs [13,14].

### Adverse Effects

Regular, heavy, or daily marijuana use and younger age at first use can lead to adverse medical, mental health, psychosocial, and cognitive outcomes, possibly due to abnormal changes in brain development. Brain maturation is incomplete until the early to mid-20s; therefore, the risk of developing problem use is greater in younger adolescents. Marijuana dose-dependently impairs a variety of psychomotor functions, including decreased reaction time, object distance and shape discrimination, time perception, perceptual-motor coordination, and motor performance. This may lead to negative outcomes such as higher rates of serious or even fatal motor vehicle crashes; poor achievement at school and work, with higher rates of school dropout; depression and anxiety; psychotic disorders, including schizophrenia in those with a predisposition toward it; and cognitive impairments, such as short-term memory loss and possible IQ decline [3].

Marijuana abuse has been linked with an “amotivational syndrome”. There is, however, little rigorous scientific evidence to support this theory [15].

Cannabis smoke contains many of the same respiratory irritants and carcinogens as tobacco smoke, although in the absence of nicotine, their effects may be moderated. Clinical and epidemiological evidence linking marijuana smoking to Chronic Obstructive Pulmonary Disease (COPD) or respiratory cancer is speculative [16,17]. Cannabis abuse may be associated with myocardial infarction, stroke and atrial fibrillation, although the absolute risk appears to be small [18,19].

A relatively rare syndrome, cannabinoid hyperemesis syndrome, involves episodic severe nausea and vomiting and abdominal pain which is relieved by exposure to hot water (shower or bath). Standard antiemetic and anti-dopamine agents are not effective, although topical capsaicin has shown some benefit [20,21].

Cannabis additionally disrupts the hypothalamic–pituitary–adrenal axis and reduces spermatogenesis, impairing several sperm functions, including motility [22].

Cannabis smoking is associated with an acutely dry mouth and irritated oral mucosa, chronic leukoplakia, inflamed oral mucosa (cannabis stomatitis), increased risk of periodontal disease (gingivitis), and oral candidiasis [23].

Under normal conditions, passive (second-hand) exposure to cannabis does not cause subjective effects or impairment.

### Risk Factors

- Risk factors of severe cannabis use disorder are as follows:
  - Younger age at first use.
  - Early and rapid progression to frequent use.
  - Concurrent use of other psychoactive substances.
  - Comorbid psychiatric disorders (for instance, depression, anxiety).
  - Stressful life events (such as childhood abuse).
  - Peer use of drugs.
  - Social isolation [24].

### Screening

Screening for marijuana use is necessary if the following symptoms were observed during history and physical exam: chronic conjunctival injection, Cannabis smell on clothing, worsening or poor response to treatment of a disease known to be intensified by Cannabis abuse like cognitive impairment, depression and anxiety, unexplained worsening in vocational, academic and social performance, unusual increase in appetite or craving of specific foods and yellowing of fingertips.

Screening for marijuana abuse can be performed using self-report questionnaires or by drug toxicology. Drug testing is more expensive but it has a higher sensitivity. Drug toxicology is usually used in high-risk patients in specialty care for substance use or in mental health clinics [25,26]. In situations such as the hiring of employees in safety-sensitive workplaces such as transportation and law enforcement, testing is also indicated. Urine toxicology always measures THC, the primary psychoactive compound in cannabis, and/or its major metabolite, carboxy-THC. Passive (second-hand) exposure to cannabis smoke rarely causes a positive drug test. A positive drug test must be confirmed with more specific tests, such as gas chromatography and mass spectrometry [27].

### Synthetic Marijuana

Synthetic cannabinoids can have more intense and long-lasting effects than natural cannabis. These effects—which may include symptoms such as tachycardia, agitation, sedation, and
psychosis—could be medically serious and require hospitalization. Acute intoxication may also cause severe cardiac and respiratory complications and seizures. Synthetic marijuana (also known as K2 and spice, among others) lacks the THC chemical structure, and is therefore not detected by standard drug screening tests [28].

Several factors have caused the intensification in these adverse effects:

• Synthetic cannabinoids are pure agonists with a very high affinity at the CB1 receptor, while THC is a partial agonist at both CB1 and CB2 receptors.
• Synthetic cannabinoids have no apparent action at non-cannabinoid receptors, whereas cannabis contains compounds which act on a variety of receptors.
• Cannabis contains compounds, including cannabidiol, which appear to counteract the effects of THC, whereas synthetic cannabinoids are pure receptor agonists [29].

Diagnosis
Cannabis use disorder-DSM-5 diagnostic criteria for cannabis use disorder are as follows:

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Cannabis taken in larger amounts or over a longer period than was intended.
2. Persistent desire or unsuccessful efforts to cut down or control cannabis use.
3. A great deal of time spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
4. Craving, or a strong desire or urge to use cannabis.
5. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued cannabis use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
7. The giving up or reduction of important social, occupational, or recreational activities because of cannabis use.
8. Recurrent cannabis use in situations in which it is physically hazardous.
9. Continued cannabis use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.

Tolerance, as defined by either of the following:

1. A need for markedly increased amounts of cannabis to achieve intoxication or desired effect.
2. A markedly diminished effect with continued use of the same amount of cannabis.

Withdrawal, as manifested by either of the following:

• Mild—presence of two to three symptoms.
• Moderate—presence of four to five symptoms.
• Severe—presence of six or more symptoms [30].

Withdrawal symptoms: Cessation of cannabis use may lead to a withdrawal syndrome in which uncomfortable symptoms serve as negative reinforcement for the resumption of cannabis use. These symptoms are usually the opposite of those caused by marijuana abuse and consist of insomnia, anorexia, anxiety, agitation, depression, and shaking. The level and duration of marijuana abuse dictate the intensity and duration of withdrawal symptoms, which are more behavioral and affective than physical [31].

Comorbidity
Cannabis use disorder has substantial comorbidity with other substance use disorders and several psychiatric disorders.

Schizophrenia
Marijuana abusers have higher rates of schizophrenia compared with nonusers. This prevalence is higher if marijuana abuser is in early adolescence, abuses more intense cannabis.

Cannabis use is one few modifiable risk factors in schizophrenia especially in those with family history of schizophrenia, subclinical psychotic patients and individuals with new impaired function [32-34].

Posttraumatic Stress Disorder (PTSD): Cannabis use disorder was associated with higher prevalence of PTSD compared with less intense cannabis use or no cannabis use. Comorbidity between these two conditions is around 10% [35].

Anxiety Disorder
Patients with anxiety disorder have higher prevalence of cannabis use compared with those without anxiety disorder (odds ratio=1.68). Cannabis intoxication can result in acute anxiety and also anxiety may be developed during Cannabis withdrawal. Management of anxiety disorder in cannabis abuser is associated with improvement of cannabis use disorder [36,37].

Other psychiatric disorders: There are higher comorbidity between cannabis use disorder and several psychiatric disorders especially Attention Deficit Hyper Activity Disorder (ADHD), Obsessive Compulsive Disorder (OCD), mood disorder and several personality disorders such as antisocial and obsessive-compulsive personality disorders [38-41].

Comorbid Cannabis use disorder and substance use disorder: Cannabis abusers have higher prevalence of alcohol, opiate, stimulant and other psychoactive drug use disorders. Cannabis use disorder usually precedes abusing of other drugs like stimulants.

A majority of daily recreational cannabis users also binge drink alcohol. Cannabis use is associated with increased likelihood of persistent alcohol use disorder over the next three years in patients with a history of alcohol use disorder [42].
Nicotine use disorder is about six times more likely in cannabis abusers [10].

Treatment

Cannabis use disorder is usually treated on an outpatient basis, but residential treatment could be necessary for patients who cannot remain abstinent in an outpatient setting or those with polysubstance use disorders.

Cannabis withdrawal symptoms may happen in about one third of heavy cannabis abusers. Although, no medication was approved by FDA to treat Cannabis withdrawal symptoms. In a clinical trial, treatment of withdrawal symptoms with dronabinol (synthetic THC 30-60 mg daily) reduced withdrawal symptoms and improved treatment retention, but did not affect subsequent cannabis use [11,43-45].

Gabapentin (1200 mg in divided doses) has shown the best results in clinical trials [46].

Because individuals taking dronabinol are likely to test positive for cannabinoids on urine drug testing, a reasonable choice for patients who may be subject to drug testing is gabapentin.

Zolpidem, a non-benzodiazepine GABA-A agonist, (12.5 mg extended release nightly at bedtime) is among the medications found to be effective in clinical trials of sleep disturbance associated with cannabis withdrawal [47].

The recommended first line therapy for cannabis use disorder is psycho-social treatment. No clinical trials comparing the efficacy of medication and psychosocial treatment exist, but some do show evidence of efficacy for psychosocial interventions, while trials of medication have yielded only inconsistent or weak results [11,46]. Between psychosocial interventions, first-line treatment should be a structured psychotherapy which is efficacious in cannabis use disorder in clinical trials such as Cognitive-Behavioral Therapy (CBT) or Motivational Enhancement Therapy (MET). The selection between these two treatments depends on patient preference and availability of these treatments.

Cognitive-Behavioral Therapy (CBT) is a psychotherapy approach which emphasizes identification and management of thoughts, behaviors, and external triggers that exacerbate substance use, followed by teaching coping and problem-solving skills that promote replacement of cannabis-related behaviors with healthier alternatives. CBT concentrates primarily on relapse prevention [47].

Motivational Interviewing/Motivational Enhancement (MET)- Motivational interviewing is a directive, patient-centered psychotherapy approach which underlines the importance of self-efficacy and positive change and attempts to build motivation for treatment and abstinence in an empathic and non-judgmental environment [48].

If these treatments are not effective, combination of these treatment or adding contingency treatment to CBT or MET, is recommended. Contingency treatment uses positive reinforcement techniques to increase specific behaviors that enhance treatment retention. Both of these approaches have improved patient’s response to psychosocial therapy in clinical trials. For cannabis abusers who have no access to one of these structured psychotherapies, it is helpful to refer them to addiction counseling and mutual help group like Marijuana Anonymous [10].

In clinical trials, the medications didn’t show any significant efficacy in the treatment of cannabis use disorder so FDA has not approved any medication in this regard [49].

Medical Marijuana

Anecdotal reports claim the successful use of medical marijuana for the treatment of a variety of health conditions including attention-deficit/hyperactivity disorder, anxiety and depression, intractable seizures, autism, chronic pain, anorexia and cachexia, glaucoma, and post chemotherapy nausea and vomiting. However, no published randomized controlled studies currently exist on the use of medical marijuana in these populations [50].

The United States food and drug administration have approved two oral formulations-dronabinol (Marinol) and nabilone (Cesamet) to treat retractive vomiting and cachexia [51]. To date, neither has been proven to have greater efficacy than other currently available medications.

Medical marijuana is most frequently prescribed for severe or chronic pain. In a variety of peripheral and central neurons that cause pain perception, CB1 receptors are distributed at high levels. CB1 agonists produce analgesia at several sites along the pathway of pain transmission (spinally, supraspinally and peripherally). Although in most placebo-controlled studies, marijuana has been proven effective for the treatment of chronic pain, five randomized, controlled, head-to-head studies failed to reveal its superiority to diphenhydramine (Benadryl), codeine, or amitriptyline for pain relief [52].

Conclusion

Cannabis use disorder can cause clinically significant dysfunction in school and work. It impairs concentration, episodic memory, attention, associative learning, and motor coordination in a dose-dependent manner. Most cases of acute cannabis withdrawal episodes are mild and there is no need for medical treatment. First-line treatment should be a structured psychotherapy which is efficacious in cannabis use disorder in clinical trials such as Cognitive-Behavioral Therapy (CBT) or motivational enhancement therapy (MET). The legal status of cannabis use, for medical and recreational purposes, varies internationally and across the United States. The patients who want to use Medical Marijuana should undergo a complete assessment, including a discussion of the risks and benefits of medical marijuana, and must be informed that it is not recommended by most major medical organizations and the insurances will not cover it.
References


