



Review Article

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Cannabinoid Acute Intoxication, Diagnosis, and Management

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ABSTRACT

Cannabis use is a common behavior among adults and adolescents, particularly after legalization in certain countries. It also reported that pediatric exposure to cannabinoid-containing products has increased for the same reason. Acute cannabinoid intoxication affects almost every part of the body, especially cardiovascular, nervous, and gastrointestinal systems, in addition to its psychoactive effects. This article aims to review the background of cannabis and its impact on the human body and review the common adverse outcomes, including the fatal consequences. Also, in this article, we aim to address the therapeutic approach of cannabinoid intoxication in the emergency setting. We used the PubMed database looking for relevant articles on the topic, addressing the emergency setting specifically. We used the following Mesh words: Cannabis, delta-9-tetrahydrocannabinol, cannabinoid intoxication, emergency department. Cannabinoid provides various body effects, but gastrointestinal and psychiatric complaints were the most common symptoms requiring emergency visits. Luckily, most of those patients do not demand hospital admission and are successfully discharged after symptomatic management. However, severe but rare symptoms must be adequately addressed, especially in concomitant use of another illicit drug, leading to respiratory depression, severe cardiovascular outcomes, or even death.

Key words: *Cannabinoid intoxication, Δ^9 -tetrahydrocannabinol, Cannabis, Cannabis adverse effect*

INTRODUCTION

Acute intoxication is defined as a pathological state resulting from the function of a naturally poisonous material or when overdosed [1]. It is a dynamic procedure that leads to short but intense and quickly worsens and may result in dangerous consequences [1]. However, cannabis is the utmost prevalently abused illicit drug, especially among young people aged between 15 and 16 in Europe [2], with approximately 128 to 238 million users worldwide [3]. It is generally considered a relatively harmless drug [4-6]. Still, certain severe reports of acute toxicity were associated [1]. Hence, it became essential to be promptly identified and therapeutically approached in the emergency setting [1]. Nevertheless, the onset age of cannabis use is decreasing, and adolescents start to use cannabis at an earlier age, which is when they become more exposed to its effects [4].

Cannabis-related adverse outcomes affect one in six adolescent cannabis users [2]. The most acute adverse effects are hyperemesis, psychosis, and anxiety [1]. Furthermore, it has been reported that some severe acute toxicity is self-limiting, such as vomiting or moderate neuropsychiatric symptoms that do not demand hospital admission and result in a short hospitalization in the emergency department [1]. Notably, regular cannabis consumption in adolescents is associated with lower school accomplishment, early school dropout, lower cognitive performance, altered brain integrity, depression, psychosis, anxiety, impulse-control disorders, and suicidal ideation [2].

RESULTS AND DISCUSSION

Cannabis endogenous effect and adverse outcomes

Though cannabis consists of various cannabinoid compositions, the primary psychoactive compound is Δ^9 -Tetrahydrocannabinol (THC) that influences the Peripheral Nervous system (PNS) and the Central Nervous System (CNS) through cannabinoid 1 (CB1) receptor agonist together with other body organs [3, 7, 8]. This receptor is part of the endogenous cannabinoid system, consisting of the metabolism of the endocannabinoids, reuptake, the biochemical machinery for synthesis, endogenous ligands, and CB2 receptors [3]. The endocannabinoid system has a physiologic regulatory effect in various procedures, such as psychiatric disease, appetite regulation, cardiovascular function, sleep and wake cycle, neural development, immune function, pain, inflammation, etc. [8].

Furthermore, endocannabinoids are endogenously lipids with precursors existing in lipid membranes that interact with endocannabinoid receptor CB1 and CB2; being lipophilic, cannabinoids are quickly absorbed [8]. The highest abundant G-protein-coupled receptor in the CNS is CB1, where CB2 receptors are primarily found on microglia but not neurons [3]. Considering that the widespread distribution of CB1 receptors in the CNS, THC creates a wide range of dose-dependent, acute psychotropic impacts, such as feeling high "euphoria" and relaxation, which is thought to be the major reason for cannabis consumption [3]. Moreover, THC has been used recreationally through various forms: vaporized, smoked, orally ingested, or even topically applied [7]. Acute cannabis intoxication includes both physical (cognitive impairment, tachycardia, conjunctival injection, and short-term memory tasks) and psychiatric effects (relaxation, euphoria, loss of inhibition, and time distortion) [7].

Besides, animal studies showed that the endocannabinoid system affects dopamine release regulation during silence attribution. Acute THC dysregulates the endocannabinoid and dopaminergic systems, leading to disorders in salience processing [9]. Chronic cannabis application is also related to a 9% risk of substance use impairments [9]. Regarding cannabis withdrawal symptoms that might require an emergency visit, including anger, irritability, or aggression, anxiety or nervousness, reduced appetite or weight loss, sleep problems, sleepiness, restlessness, depression, and physical symptoms were leading to great discomforts, like tremor or shakiness, fever, chills, headache, and sweating which usually occurred 48 hours after cessation [9]. Significantly, the severity of withdrawal symptoms is directly related to a more significant negative effect on normal daily activities, which suggest that the impact of cannabinoids withdrawal look equal to other substance abuse withdrawal [9]. Withdrawal symptoms are usually resolved within 2 to 12 weeks.

Cannabis-related emergency visit in pediatric population

In the pediatric population, cannabis use has a significant impact, especially following legalization in the United States, especially in the last five years [10, 11]. The decriminalization of medical and recreational cannabis use in the United States resulted in increased emergency department visits from unintentional pediatric cannabis intoxication [10]. Exploratory or unintended cannabis-containing products consumptions by children can result in considerable pediatric toxicity, such as respiratory depression, coma, and encephalopathy [10]. Also, cannabis is the most common substance usage among antipart women, and the estimated prevalence is between 3% and 16% in the United States [8]. From 2002 to 2014, per-month the use of cannabis among antipart women has enhanced by 62%, particularly after legalization in the United States that enhanced accessibility and strengthened advocacy for its usage [8]. Cannabis use among youth often engages in other risk-taking behaviors that affect overall health; for instance, 13% of youth reported driving after cannabis use [8]. Furthermore, driving under cannabis influence doubles the risk of a fatal road accident.

Emergency department visits secondary to cannabis toxicity have enhanced in adolescents and adults, with doubled rates in those aged 12 to 17 years between 2004 and 2011, and also in the pediatric population after producing new cannabis edibles, such as hemp oil, candy, popcorn, and beverages [10, 12]. Also, parents' outbreak of cannabis usage with their children at home has risen from 4.9% to 6.8% from 2002 to 2015 and increased in the call volume to poison control centers for unintentional pediatric cannabis exposure [11, 13]. This rise in pediatric unintentional cannabis intoxication is likely multifactorial: it is mostly associated with diverse modes of delivery, increased availability, and improved palatability of cannabis [10]. In addition, for the last few decades, the potency of cannabis-containing products has dramatically enhanced [10].

Nonetheless, acute cannabis intoxications in the adolescent populations resulted in various symptoms, including raised appetite, nystagmus, conjunctival injection, slurred speech, dry mouth, and ataxia [11]. Vital instability might result from acute cannabis intoxications, including hypertension, tachypnea, and tachycardia [11]. High-

potency cannabinoid products might cause hallucinations, anxiety, or dysphoria [11]. Intense cannabis intoxication and physiologic alteration can be caused by exposure to other recreational drugs [11]. Therefore, secondary to the public magnitude of cannabis use, particularly after legalization in certain countries, the emergency physician must provide an early recognition, management, evaluation, and counseling of suspected pediatric unintentional cannabis ingestion [10].

Severe cannabis-related adverse outcome requiring emergency admission

Overall, cannabis use alone usually does not demand an emergency visit. However, severe symptoms might emerge when cannabis use is concomitant with other substances, especially psychoactive substances (approximately 1/4 of the cases), and emergency admission might be needed [13]. Cannabis use alone mostly leads to minor toxicity with neurobehavioral symptoms, including panic attacks, nausea, anxiety, cardiovascular activation, and vomiting [13]. There are rare but severe complications, such as coma, and other cases require intubation and intensive care unit admission or psychiatric care [13]. When cannabis is used and other substances (usually alcohol followed by cocaine), this often leads to moderate to severe complications, including lower GCS scores that require therapy and admission to the psychiatric or intensive care unit [13].

Though no mortality was noticed in both groups, patients with combined use were more often presented with hallucinations, agitation, and respiratory depression than cannabis use alone. In contrast, the latter is commonly presented with palpitation, panic attack, anxiety, and chest pain [13]. Nevertheless, sudden unanticipated death was reported under the acute effect of cannabis in two young males without significant past medical history [14]. Based on a retrospective observational study, emergency admission following cannabis intoxication was 31% of overall substance abuse intoxications and was more frequently reported in younger adult males [13].

Cardiovascular outcomes secondary to cannabis intoxications include tachycardia and systolic blood pressure, especially when combined with other substances, and a quarter of the admitted patients experienced palpitations [13]. In crossover research, various accounts of cardiovascular mortalities after cannabis use and a mildly enhanced hazard of myocardial infarction were reported within one hour after cannabis smoke [13]. Also, some authors consider that cardiovascular toxicity and death after cannabis use are uncommon but underrecognized [13].

Moreover, chest pain was observed in 15% of lone-cannabis patients and was significantly more common among cannabis users with other substances [13]. Pneumothorax has been reported in both groups of cannabis alone who presented with chest pain [13]. In a systematic review, the risk of spontaneous pneumothorax was found more in combined cannabis and tobacco users [13]. In addition, the risk of arrhythmia, including Brugada syndrome and atrial tachyarrhythmias, were also raised in cannabis users, particularly when combined with tobacco smoke [13]. Following smoking cannabis alone, a 27-year-old woman developed supraventricular tachycardia and required adenosine for sinus rhythm restore [13]. Additionally, unintentional ingestion of cannabinoid edibles resulted in acute seizure attacks in two 3-years-old children [15].

A retrospective, observational study comparing emergency visits related to edible and inhaled cannabis exposure showed that hospital admission due to inhaled cannabis was more common than edibles [16]. Hospital admission was primarily attributed to cannabinoid hyperemesis syndrome (CHS), which is far more common among inhaled cannabinoids than edibles [16]. On the other hand, the latter was associated with more acute psychiatric events and cardiovascular symptoms than inhaled exposure and more emergency visits than expected [16].

CHS is a clinical syndrome characterized by recurrent episodes of intense nausea and vomiting and abdominal pain remarkably relieved by hot showers [17]. Standard anti-emetic medications are often insufficient in symptomatic control [17]. However, although CHS develops after years of TCH-containing products exposure, it might occur in the pediatric population [17]. Capsaicin, the defining chemical in hot peppers, has been successfully applied as a topical therapy for symptomatic control in adults [17]. Capsaicin depletes substance P secondary to agonism of TRPV-1 receptor [17]. Besides, capsaicin proved efficacious relief of CHS in the pediatric population [17].

Emergency approach for acute cannabinoid intoxication

Obtaining a detailed medical background is necessary for various reasons: firstly, the patient may provide inaccurate history, be unreliable, and sometimes purposely deceitful. Secondly, the patient may intentionally provide false history due to the fear of legal repercussions and potential grounds for prosecution [18]. Physical examinations, looking for cannabinoid intoxications, may vary based on the route of administration [18]; however, clinical signs of cannabinoid intoxications are well-known and established, as mentioned above.

The emergency physician must start with an established good relationship with the patient to obtain further detailed history as possible. Ordinarily, a urine drug screen (USD) is the most commonly used method for cannabinoid intoxication screening, which is an immunoassay detecting Δ^9 -THC metabolites 11-nor- Δ^9 -tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC) [19]. 9-carboxy-THC is usually detectable in plasma after THC inhalation within minutes but can take several hours if ingested [19]. Typically, it is noticeable for 1-2 days up to 4 days in infrequent cannabis users but may last two weeks in daily users and over four weeks in long-term heavy cannabinoid smokers [18, 19]. On the other hand, 9-carboxy-THC can be detected within 1 hour in the urine after TCH consumption [19]. Nonetheless, a positive urine test is non-specific and can indicate cannabis consumption from 1 hour to several weeks [19].

Additionally, certain substances were found to be associated with a false-positive urine test, such as help containing food, proton pump inhibitors, promethazine, dronabinol, some non-steroidal anti-inflammatory drugs, and efavirenz [19]. THC can be certified by mass spectrometry, gas chromatography, or high-performance liquid chromatography [18, 19]. In addition, it can be diagnosed in the blood, saliva, or hair testing, but these are inappropriate in the emergency setting due to inaccuracy and time-consuming [19]. Stomach contents may also be sampled for cannabinoids, and toxicologist consultation or diagnostic toxicology laboratory is suggested before sample collection and submission of any specimens [18].

While most patients presented to the emergency with gastrointestinal, psychiatric complaints, or intoxication, these patients often do not require hospital admission [20]. Other complaints, including dermatological, respiratory, trauma, and cardiovascular, had the highest hospital admission rate, suggesting that these patients are severely ill than the gastrointestinal or psychiatric complaints [20]. Patients with gastrointestinal symptoms are likely to receive anti-emetics and anti-nausea medications, which usually control their symptoms [20]. In contrast, patients who presented with psychiatric complaints are likely to receive symptomatic treatment in the emergency department and are generally discharged without further medical complaints [20].

There has been no specific medication certified by the FDA to treat cannabis use disorders, including intoxication [21]. Several promising studies suggest that N-acetylcysteine acid and CB1 agonists might help treat cannabinoid withdrawal craving behaviors [21]. Further, dronabinol, a schedule III synthetic THC, was beneficial in treating nausea and cachexia through partially agonizing CB1 receptors [21]. Additionally, propranolol in the dose of 120mg was found to reduce the subjective intoxication effects when administered one hour after the use of cannabis. Also, there are possibilities that the THC effect on the brain might be partially affected by beta-receptors [22]. Rimonabant, a selective CB1 antagonist, has been shown to block the THC physiologic (mainly cardiovascular) and subjective intoxication effect [9, 22]. Flumazenil and cannabidiol were also shown to counteract the impact on comatose and anxious and psychotic states, respectively, although further review is needed to strengthen this regard [22].

CONCLUSION

Cannabis is a commonly used illicit drug, especially after legalization in certain countries, including the United States. Acute cannabis intoxication is a common reason for emergency admission and might require medical treatment and observation. Although most common emergency presentations are due to gastrointestinal and psychiatric complaints, patients are usually discharged home after symptomatic therapy with no further medical complaints. Nevertheless, specific severe but rare adverse outcomes have been reported with cannabis intoxications, requiring the emergency physician's early recognition and special attention. Some cases reported admission to the intensive care unit and might need respiratory support. Importantly, the emergency physician must be familiarized with cannabis intoxication symptoms, particularly in the era of cannabis use decriminalization and when combined with other substances that lead to severe and sometimes fatal consequences.

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