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Acute pancreatitis as a rare adverse event among cannabis users

A systematic review

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Abstract

Background: Cannabis use has been steadily rising in the United States and can have multiple adverse effects, including cannabis-induced acute pancreatitis. This study aims to collate and highlight the significant demographics, clinical presentation, and outcomes in patients with cannabis-induced acute pancreatitis.

Method: A systematic literature search of electronic databases for peer-reviewed articles was conducted. After an initial search, we found 792 articles through different electronic databases. After manually removing duplicates and articles that did not meet the criteria, 25 articles were included in our review.

Results: A total of 45 patients were studied, 35 (78%) cases were male and 10 (22%) cases were female, showing male predominance. The mean age of all participants was 29.2 ± 10.3 years. The most common presenting symptoms were abdominal pain 21 of 21 (100%), nausea 17 of 21 (81%), and vomiting 12 of 20 (60%). Ultrasound was normal in the majority of patients, with findings of mild pancreatitis. Computerized tomography scans revealed pancreatic edema and inflammation in 7 of 20 (35%) patients, and findings of necrotizing pancreatitis and complex fluid collection were visualized in 3 of 20 (15%) patients. Dilatation of intrahepatic or extrahepatic biliary ducts was not seen in any patients. The overall prognosis was good, with reported full recovery.

Conclusions: Cannabis should be included in the differential diagnosis for the etiology of acute pancreatitis, which would help in early intervention and treatment for the mitigation of the rapidly progressive disease.

Abbreviations: CBD = cannabinoids, CIP = cannabis induced pancreatitis, GMCSF = Granulocyte macrophage colony stimulating factor, HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome, IL = interleukin, THC = tetrahydrocannabinol, WBC = white blood cells.

Keywords: acute pancreatitis, cannabis, pathology

1. Introduction

Cannabis is the most widely used illicit drug globally. Weed can be described as a hallucinogen, depressant, or stimulant due to varying effects from person to person. Tetrahydrocannabinol (THC) is the substance present in cannabis that overactivates specific brain receptors and primarily affects users' mental states. It is now being used legally as a recreational drug and for medical purposes by more than half of the United States.[1] Drugs containing cannabinoids are being used for treating a multitude of illnesses, namely epilepsy, chemotherapy-induced nausea, posttraumatic stress disorder, Tourette syndrome, inflammatory

DM and NB contributed equally and are joint second authors.

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All data relevant to the study are included in the article or uploaded as supplementary information.

As all the data were taken from published literature from database. Hence, there was no requirement for ethical approval by any institute.

Patients and the public were not involved in this research's design, conduct, reporting, or dissemination plans.

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Key points

- Our study shows male predominance with a 4:1 ratio among patients diagnosed with acute pancreatitis post cannabis use.
- Majority of the cases belonged to the younger age group (mean age: 29.2 years).
- Overall prognosis was good, and management was mostly conservative with a good recovery rate.

bowel disease,[2] human immunodeficiency virus/acquired immune deficiency syndrome-induced weight loss and loss of appetite,[3] multiple sclerosis,[4] and chronic pain among others.[5]

About 147 million people, 2.5% of the world population, consume cannabis.[6] The majority of these users fall in the age group of 18 to 25 years.[7] Cannabis is associated with the development of mild adverse effects like dizziness, nausea, dry mouth, and somnolence. Severe adverse effects related to cannabis use are depression, disorientation, anxiety, seizures, schizophrenia, other psychosis, gastrointestinal diseases, and cardiovascular diseases.[8] Smoking cannabis during pregnancy has been attributed to low birth weight. It has also been linked to the increased incidence of motor vehicle accidents. A rare presentation of cannabis-induced acute pancreatitis has come to light in the last couple of years. There is only limited literature available in case reports and case series. Mortality for pancreatitis is 1% overall; however, this number reaches as high as 30% to 40% in hospitalized patients.[9]

With this systematic review, we highlight the critical key clinical findings, duration, outcomes, and demographic details of cannabis-induced pancreatitis.

2. Methods

This systematic review was conducted and reported in conformity with the Cochrane and Preferred Reporting Items for Systematic Review and Meta-analysis 2020 guidelines.[10] A prespecified protocol has been registered on PROSPERO (CRD42022300912).

2.1. Search strategy

We conducted a systematic literature search in PubMed, Embase, Google Scholar, and Scopus using predefined MESH terms by using "AND" and "OR". The following search terms were used: "Cannabis" OR "Marijuana" AND "Acute Pancreatitis" OR "Pancreatitis" OR "Addictive Drugs" AND "Outcomes." We queried databases from their inception to April 15, 2022, without restriction on the language of the studies. All the studies were carefully screened and exported to the Endnote 2020 library (X9). A manual check was carried out to remove duplicates. Two reviewers (D.M. and N.B.) reviewed the titles and abstract. Discrepancies regarding inclusion of studies were arbitrated by senior author (V.J.).

2.2. Eligibility criteria

The following criteria were used for inclusion: studies with an age group >18 years, either case reports, case series, and prospective or retrospective studies of those who developed acute or chronic pancreatitis after consuming cannabis. Studies that involved animal testing, review articles, studies on patients of <18 years of age, and studies with a mix of cannabis and other etiology as a cause for pancreatitis were excluded.

2.3. Study selection and characteristics

We included studies with a history of cannabis use with the diagnosis of acute pancreatitis. The studies were carefully screened and exported to the EndNote references library software (Clarivate), and all the duplicates were removed. A manual check was carried through to crosscheck for any remaining duplicates. A total of 792 articles were extracted in the initial screening. Two reviewers (V.J. and D.M.) reviewed the articles that passed the initial screening to regulate their aptness for inclusion in the systematic analysis. The senior author arbitrated discrepancies regarding the inclusion of studies.

2.4. Data extraction and analysis

The following data were extracted from the studies: demographic data (study design, country, gender, and age), comorbidity, risk factors, symptoms, laboratory data, and imaging data. Three authors assembled all available information in a shared spreadsheet (N.B., D.M., and V.J.). If any required data were missing, written in an incorrect format, or not reported in the article, the corresponding authors of the respective articles were contacted via email for clarification. Supplementary material related to the main article was also investigated in such cases. Finally, descriptive statistics was used to summarize the data in this article. The median and interquartile ranges were adopted to describe continuous variables, whereas frequencies and percentages were used for dichotomous data. All statistical analyses were conducted using the software R version 4.1.2 (available at https://cran.r-project.org).

3. Results

3.1. Study selection

A preliminary database search using the keywords yielded 792 articles, of which 453 studies were duplicates. One hundred ninety-eight studies were further excluded after the initial title and abstract screening. A full-text review was conducted for the remaining 70 articles. Forty-five studies were further excluded based on exclusion criteria. A total of 25 studies that met the eligibility criteria were included in our systematic analysis (Fig. 1). Among the 25 studies, 22 studies were case reports, whereas 3 were case series in design.

3.2. Baseline characteristics of included patients

Of the 25 studies identified, 45 patients were identified to have developed acute pancreatitis after using cannabis, there was no reported history of recent alcohol use and/or gallstones on imaging in these patients, and no other obvious cause of pancreatitis was present. There was a gender difference among the patients diagnosed with acute pancreatitis post cannabis use, with 35 (78%) male cases and 10 (22%) female cases. Mean age (±S.D.) of patients was 29.2 ± 10.3 years. Twenty-two (49%) patients were from France, 12 (27%) from the United States, 2 (4%) each from Italy, Turkey, Croatia, and 1 (2%) each from the United Kingdom, India, Iran, Tunisia, and Spain (Table 1; Table 1, Supplemental Digital Content, http://links.lww.com/MD/G834).

3.3. Comorbidity and risk factors

Among all reported cases of acute pancreatitis, 16 cases have shown comorbidity findings, which include diabetes mellitus 2 of 16 (12.5%) and hypertension, hyperlipidemia, gastroesophageal reflux disease, diverticulitis, and meningitis, 1 case each, that is, 1 of 16 (6%; Table 1; Table 2, Supplemental Digital Content, http://links.lww.com/MD/G834).

Data on different risk factors are reported variably and are as follows: 45 of 45 (100%) cannabis users, history of tobacco smoking was found in 9 of 25 studies, that is, 20 of 28 patients (71%), and alcohol consumption was reported in 4 studies, 2 of 6 patients (33%) had a positive history (Table 1). Cannabis use, smoking, and alcohol consumption were the 3 most common risk factors reported, leading to acute pancreatitis.

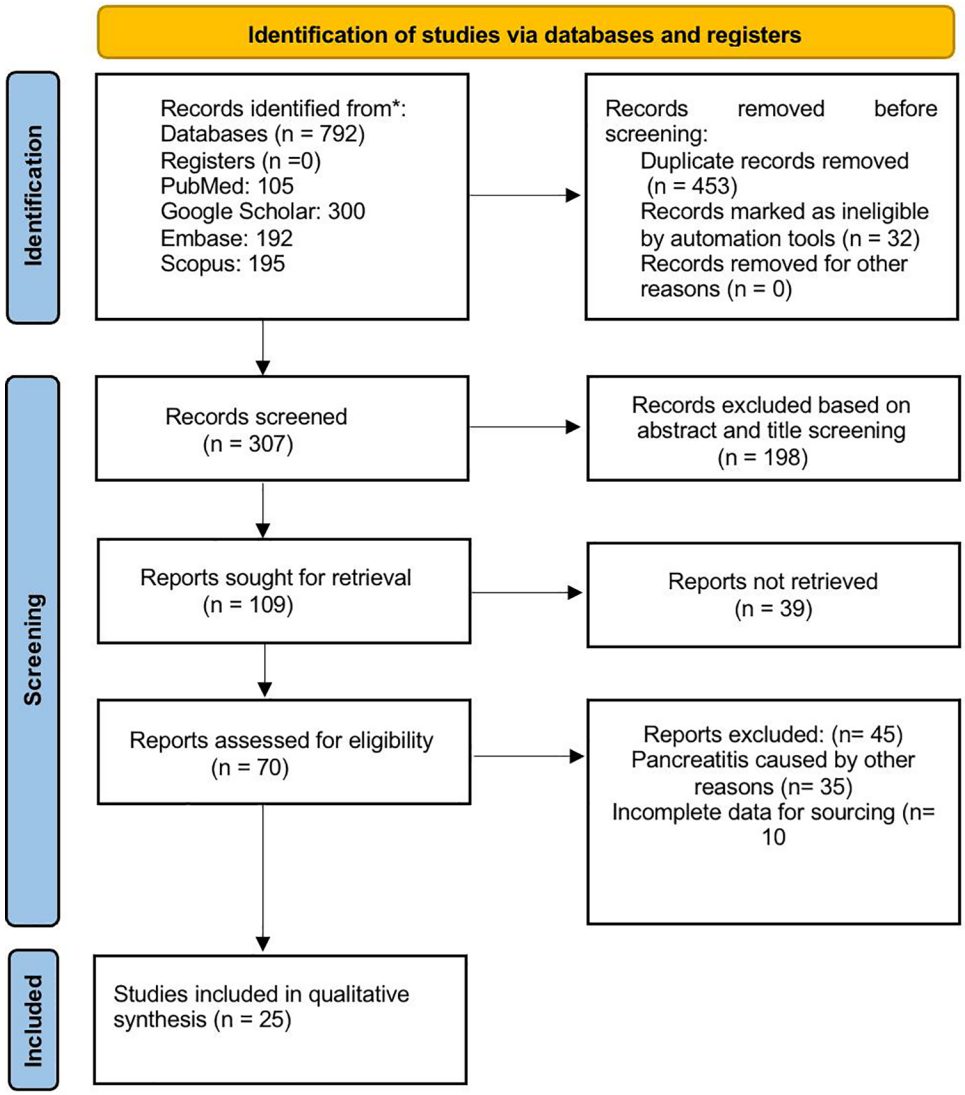

Figure 1. PRISMA flow diagram for study screening and study selection process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.4. Symptoms

Data on symptoms were variably reported in 18 studies, thus making the total number of patients with a particular symptom different for each. The proportion of each symptom was 21 of 21 (100%) abdominal pain, 17 of 21 (81%), nausea, 12 of 21 (57%), vomiting, 1 of 20 (5%) seizure, and 1 of 21 (5%) diarrhea (Table 1; Table 2, Supplemental Digital Content, http://links.lww.com/MD/G834).

3.5. Laboratory findings

Laboratory data of patients were obtained from 24 studies. The levels of the each lab variables were expressed as median and interquartile range and were as follow: white blood cell count: 15 (13–17) × 10^9 L, creatinine: 0.9 (0.86–0.89) mg/dL, glucose: 129 (121–168) g/dL, aspartate aminotransferase: 19 (17–27) U/L, alanine aminotransferase: 27 (23–47) U/L, total bilirubin: 0.65 (0.48–0.83 mg/dL) mg/dL, serum amylase: 567 (321–952) U/L, and serum lipase: 900 U/L (428–1081) U/L (Table 1; Table 3, Supplemental Digital Content, http://links.lww.com/MD/G834).

3.6. Imaging findings

Ultrasound findings were obtained from 16 out of 25 studies, that is, 19 patients. Ultrasound in 2 of 19 patients revealed mild pancreatitis, 2 of 19 patients had pancreatic enlargement and edema, and in 3 of 19 patients, the pancreas could not be visualized due to overlying bowel gas. Dilatation of intrahepatic or extrahepatic biliary ducts was not seen in any patients. Normal ultrasound findings were reported in 12 of 19 patients (Table 1; Table 4, Supplemental Digital Content, http://links.lww.com/MD/G834).

Computed tomography (CT) findings were reported in 17 of 25 studies with 20 patients. Pancreatic edema and inflammation were seen in 7 of 20 patients, localized in the head in 1 patient. Peripancreatic fat inflammation and stranding were seen in 3 of 20 patients; 2 of 20 scans revealed necrotizing pancreatitis, 1 of which was distal, and the other involved both pancreas and liver. The hepatopancreatic necrosis was associated with intraperitoneal effusion. Complex fluid collections associated with inflamed pancreas were seen in 2 of 20 patients. Normal CT scans were reported in 8 of 20 patients (Table 1; Table 4, Supplemental Digital Content, http://links.lww.com/MD/G834).

Magnetic resonance imaging (MRI) findings were obtained from 9 of 25 studies, that is, 9 patients. In 1 patient, MRI revealed pancreatic necrosis with acute complex fluid collection and absence of biliary dilatation. Mild stranding of peripancreatic fat was seen in 1 patient. Magnetic resonance cholangiopancreatography showed 1 patient's pancreatic duct enlargement

Table 1

Summary table highlighting the baseline, demographic, and clinical outcomes among all included studies.

Variables	N = 45
Age (mean, SD)	29.25 ± 10.31
Gender	
Male, n (%)	35 (78%)
Female, n (%)	10 (22%)
Country	
United States	12/45 (27%)
France	22/45 (49%)
Italy	2/45 (4.4%)
Turkey	2/45 (4.4%)
Croatia	2/45 (4.4%)
United Kingdom	1/45 (2.2%)
India	1/45 (2.2%)
Iran	1/45 (2.2%)
Tunisia	1/45 (2.2%)
Spain	1/45 (2.2%)
Comorbidity	16 patients
Diabetes mellitus	2/16 (12.5%)
Hypertension	1/16 (6%)
Hyperlipidemia	1/16 (6%)
Gastroesophageal reflux disease	1/16 (6%)
Diverticulitis	1/16 (6%)
Meningitis	1/16 (6%)
Risk factors	
Smoking	20/28 (71%)
Cannabis user	45/45 (100%)
Alcohol user	2/6 (33%)
Symptoms	
Abdominal pain	21/21 (100%)
Nausea	17/21 (81%)
Vomiting	12/21 (57%)
Seizure	1/21 (5%)
Diarrhea	1/21 (5%)
Laboratory findings at admission	
WBC count, median (IQR)	15 (13–17)
Creatinine, median (IQR)	0.9 (0.86–0.89)
Glucose, median (IQR)	129 (121–168)
Aspartate aminotransferase	19 (17–27)
Alanine aminotransferase	27 (23–47)
Total bilirubin	0.65 (0.48–0.83)
Serum amylase	567 (321–952)
Serum lipase	900 (428–1081)
Diagnosis of pancreatitis	
Modified Atlanta score: 2/3 score, n (%)	23 (64%)
Modified Atlanta score: 3/3 score, n (%)	13 (36%)
Radiological findings	
Ultrasound	N = 19
Mild pancreatitis	2/19 (11%)
Pancreatic enlargement and edema	2/19 (11%)
Pancreas was not visible	3/19 (16%)
Normal	12/19 (63%)
Computed tomography	N = 20
Pancreatic edema and inflammation	7/20 (35%)
Peripancreatic fat inflammation	3/20 (15%)
Complex fluid collection	2/20 (10%)
Necrotizing pancreatitis	2/20 (10%)
Normal	8/20 (40%)
Management	N = 16
Supportive	7/16 (44%)
IV fluids	7/16 (44%)
Analgesic	8/16 (50%)
Sedatives	1/16 (6.2%)
Outcomes	
Recovered, n (%)	40/40 (100%)
Mortality, n (%)	0

IQR = interquartile range, IV = intravenous, SD = standard deviation, WBC = white blood cell.

with normal biliary duct and pancreatic parenchyma. Magnetic resonance cholangiopancreatography revealed a pseudocyst 15 cm in diameter in 1 patient. Normal findings were seen in MRI scans of 5 of 9 patients (Table 1; Table 4, Supplemental Digital Content, http://links.lww.com/MD/G834).

3.7. Diagnosis of acute pancreatitis

Revised Atlanta Classification has been used in 18 studies for diagnosis of acute pancreatitis, that is, abdominal pain suggestive of pancreatitis, serum amylase or lipase level >3 times the upper normal value, or characteristic imaging findings. Twenty-three of 36 [64%] cases had 2/3 scores, while 13 of 36 [36%] cases had 3/3 scores (Table 1).

3.8. Management and outcomes

Management data were obtained from 15 studies, and the proportion of each patient with different management strategies are as follows: 7 of 16 (44%) supportive therapy, 7 of 16 (44%) intravenous fluids, 8 of 16 (50%) analgesic, and 1 of 16 (6.2%) sedatives were used. The overall prognosis was good with 40 of 40 (100) cases whose data were reported fully recovered and were not associated with any mortality (Table 1; Table 4, Supplemental Digital Content, http://links.lww.com/MD/G834).

4. Discussion

In this systematic review involving 45 patients with cannabis-induced pancreatitis, males tend to have a higher predominance of cannabis induced pancreatitis , with the most common symptoms including abdominal pain 21 of 21 (100%), nausea 17 of 21 (81%), and vomiting 12 of 21 (57%). Necrotizing pancreatitis and complex fluid collection were visualized in 3 of 20 patients. All patients recovered with conservative management with no associated mortality and also the patients were in constant follow up. Ceasing of cannabis use is the key treatment in the mentioned cases.

Cannabis was first reported as a potential cause of acute pancreatitis in 2004 by Grant and Gandhi.[11] Recent studies have found an association between increased incidence of acute pancreatitis in individuals consuming cannabis. A cohort study in Chicago of 460 patients with acute pancreatitis showed that 10% were cannabis users and 2% could attribute cannabis use as the cause of acute pancreatitis.[12] Cannabis-induced acute pancreatitis usually occurs in younger patients, with around 92.3% in <35 years of age.[13] The only prospective study regarding cannabis use and pancreatitis showed that cannabis alone accounted for about 13% of cases of acute pancreatitis <35 years of age.[14] This is similar to the findings in our study, where the mean age of incidence is 29.25 years. Cannabis could be the potential causative agent in pancreatitis categorized as idiopathic pancreatitis. Cannabis has also been associated with increased post endoscopic retrograde cholangiopancreatography pancreatitis.[15]

The endocannabinoid system consists of endogenous cannabinoids, cannabinoid receptors mediated by G protein-coupled receptors CB1, CB2, and enzymes. CBD treatment significantly reduces the level of cytokines involved in the immune response, such as interleukin (IL)-4, which inhibits T helper type 1 cells differentiation, and IL-5, which causes eosinophilic maturation. They also decrease T helper type 17 inflammatory autoimmune phenotype, downregulate the expression of pathogenic IL-17 and IL-6, and increase anti-inflammatory cytokines IL-10.[16] The G-coupled receptors CBR1 and CBR2 have been identified in pancreatic tissues and participate in the inflammatory cascade. CB1 activation is associated with fibrosis, and CB2 is associated with antifibrogenic activities in the pancreas.[17,18] THC binds to these receptors and activates endocannabinoid production, identified in acute pancreatitis.[17–22]

There have been contradicting evidence regarding the effect of the endocannabinoid system on pancreatitis. Matsuda et al[21] have reported improved survival of rats with acute pancreatitis with downregulation of the endocannabinoid system using a CB1 receptor inhibitor AM251. On the contrary, Michalski et al[23] and Li et al[24] showed that synthetic agonists of cannabinoid receptors HU210 and O-1602 have therapeutic potential in acute pancreatitis.

The first endocannabinoid was derived from arachidonoyl ethanolamide, which comes from the word anandamide, or internal bliss in Sanskrit. Anandamide inhibits the proliferation of lymphocytes and tumor necrosis factor activities.[25] Intraperitoneal administration of anandamide was associated with worsening pancreatitis in rats in a dose-dependent manner with increased incidence of pancreatic edema, inflammatory infiltrates, lipase, amylase, poly C nuclease, and interleukin 1 beta.[22] However, anandamide has protective properties against a stress-induced ulcer in the stomach, deciphering that cannabinoids have unique proinflammatory properties toward the pancreas compared to other areas of the gastrointestinal system. Anandamide has been reported to have a biphasic effect on acute pancreatitis through the sensory nerves. Studies have shown that administration of anandamide before the induction of pancreatitis is associated with aggravation of pancreatic damage, while administration after the induction of pancreatitis is associated with reduced severity.[26]

Studies have also shown that cannabis users who drink alcohol have decreased acute and chronic pancreatitis.[27] Alcohol increases the absorption of THC, and some cannabis users might consume less alcohol while consuming cannabis. Nair et al reported that alcohol abuse is associated with a higher level of inflammatory cytokines such as IL-10, IL-12, IL-15, IL-309, and GMCSF, while cannabis abuse has lower activation of these cytokines.[16] The interaction between cannabis and alcohol still needs further understanding.

Diagnosis of acute pancreatitis is based on clinical, laboratory, and imaging results. Our studies show that ultrasound examination is less sensitive than CT and MRI findings. The unknown confounding factor includes the body habitus of the patient and the experience of the radiologist, which could also play a role in the reporting of the imaging findings. Ultrasound although is one of the first tests to perform upon admission, the utility of this study is usually reserved to confirm or exclude the presence of stones and biliary dilation.[28]

In our study, another important finding is that all the patients recovered from acute episodes of pancreatitis once cannabis was discontinued. The patient population being younger, male, and lower body mass index might be a few factors that could potentially make the case fatality rate potentially to zero. A recent study has shown that cannabis-induced pancreatitis is associated with lower age-adjusted morbidity, mortality, and hospitalization cost compared to noncannabis-exposed patients.[12]

Cannabis could have a potential role in pain management for chronic pancreatitis. Medical cannabis use in 8 patients with chronic pancreatitis was associated with a reduction in daily opiate dose, hospitalization, and emergency room visits.[29] This could be due to a different pathophysiologic mechanism for neuromodulation in chronic pancreatitis with fibrosis compared to acute inflammatory cytokine cascade in acute pancreatitis.[30] Studies suggest that cannabis downregulates tumor necrosis factor-alpha and deactivates proinflammatory p38 mitogen-activated protein kinase, mammalian target of rapamycin, and promitogenic extracellular signal-regulated kinase pathway.[12]

5. Limitations

Our analysis has several limitations: the sample size is small as most of the studies previously reported are all case reports and series, missing or incomplete data relevant for inclusion of the articles, reports with pancreatitis of other etiologies, and idiopathic is another etiology of pancreatitis, which cannot be ruled out in patients with cannabis-induced pancreatitis

6. Conclusion

In conclusion, a large number of cases of cannabis-induced acute pancreatitis have been reported since the legalization of cannabis consumption. An excellent social history is essential while assessing the intake of cannabis and its potential cause as pancreatitis. Cannabis should be included in the differential diagnosis for the etiology of acute pancreatitis, which would help in early intervention and treatment for the mitigation of the rapidly progressive disease.

Physicians and health care providers need to be aware of such complications of cannabinoids, which have not been well reported until now and warrant further large-scale studies for possible pathophysiology and outcomes.

Author contributions

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