

Marijuana: A systems-based primer of adverse effects associated with use and an overview of its therapeutic utility

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Abstract

Marijuana use is on the rise in the United States. By the end of 2019, 33 states have legalized marijuana use and marijuana byproduct use for medical purposes. However, marijuana use does not come without side effects. This manuscript reviews the increasing usage of marijuana and the different forms (natural and synthetic) that patients may use when presenting to clinicians. It also addresses the biochemical and behavioral changes observed with marijuana use, including the location and changes associated with cannabinoid receptors (abbreviated CB1 and CB2). These two topics lead into an extensive review of the side effects of marijuana use. This manuscript discusses gastrointestinal side-effects, such as Cannabinoid Hyperemesis Syndrome, pancreatitis, and hepatotoxicity. It also briefly reviews cardiovascular, neurologic, and pulmonary side effects. This article provides an overview of therapeutic effects of marijuana including the antiemetic effect, its medical utility as an appetite stimulant, and usefulness in cancer patients post-chemotherapy. A thorough social history pertaining to marijuana use is an important consideration for clinicians in patients presenting with a variety of symptoms, including those effecting the gastrointestinal, cardiovascular, pulmonary, or neurologic systems.

Keywords

Epidemiology/public health, gastroenterology/hepatology, pharmacoepidemiology/drug safety, cannabis, side effects

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Introduction

Marijuana is one of the most common substances used worldwide, perpetuated by the perception that marijuana has the least amount of side effects and long-term sequelae compared to other substances.¹ Marijuana use in the United States has dramatically increased over the past several decades, with consistent increases in use since the year 2007.² For example, a cohort study from 1998 reported that only 2% of teenagers born between 1930 and 1940 experimented with the drug, while a staggering half of the questioned population born between 1956 and 1965 reported trying marijuana in their teenage years.³ Today, it is estimated that approximately 4.7% of all Americans use marijuana on a daily or near-daily basis.² In the 2016 National Survey on Drug Use and Health, 118,524 people over the age of 12 years reported

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marijuana use, with that number rising in 2017 to 122,943 people.⁴ The highest reported use of marijuana was in White males over the age of 26 years, although use is common among women of childbearing age as well.^{4,5}

Increases in marijuana usage in the United States are largely due in part to the legalization of marijuana for both medicinal and recreational purposes. By the end of 2019, 33 states had approved legislation allowing for the use of marijuana for medical purposes.² In addition, 11 states, as well as the District of Columbia, have allowed for non-medical usage of marijuana by adults aged 21 years and older.² Many states that have not fully legalized marijuana for medical treatment purposes have approved a government regulated, publicly available medical marijuana treatment program, of which patients wishing to explore the therapeutic benefits can take full advantage as well.⁶ It is important to consider that the legalization and liberalization of marijuana use may lead to a decreased perception of

risk regarding regular use of cannabis. In fact, between 2012 and 2018, the risk perception regarding the occasional use of marijuana in high school students has declined.² While there are numerous benefits to the use of marijuana for medical purposes, many of which are discussed in this manuscript, its use does not come without side effects. Because of this, it is important for clinicians to understand the various presentations of side effects associated with acute and chronic marijuana use. In this article, we provide a system-based primer of the adverse effects associated with the use of marijuana, in addition to providing an overview of its therapeutic utility in several disease processes.

Methods

A literature review was performed for articles related to the consequences of marijuana use. We used PubMed, Google Scholar, and Web of Science to search for published articles,

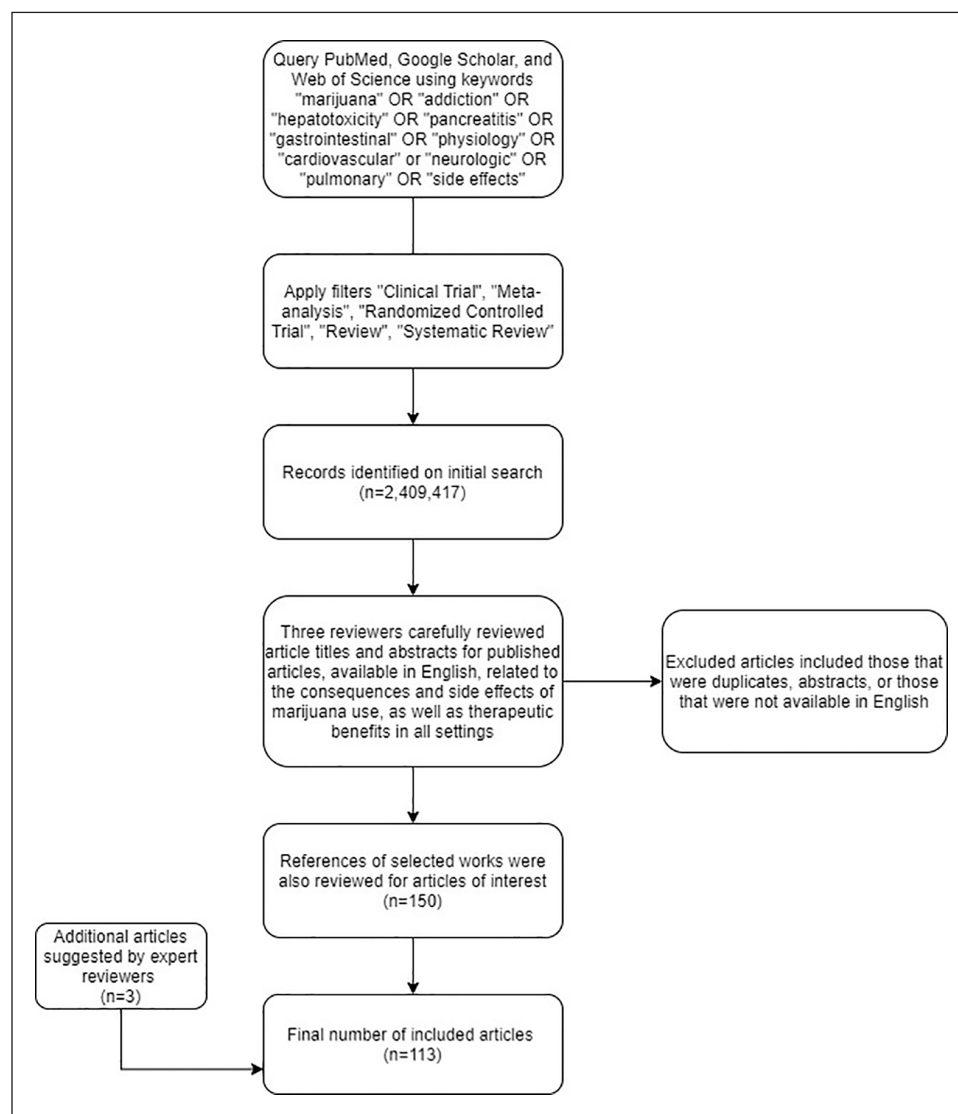


Figure 1. Flowchart describing the process of literature review.

including review articles, meta-analysis, systematic reviews, randomized controlled trials, clinical trials, case reports, or case series related to our topic. Searches through the references of retrieved articles were also performed. Based on the topic of this study, key words such as “marijuana,” OR “addiction,” OR “hepatotoxicity,” OR “pancreatitis,” OR “gastrointestinal,” OR “physiology” OR “cardiovascular” OR “neurologic” OR “pulmonary” OR “side effects” were used. Initial search returned 2,409,417 results. Article titles and abstracts were reviewed by three reviewers, who collected a total of 150 articles relative to the topic of interest. Through careful selection we narrowed the final number of articles for our review to 113. Inclusion criteria consisted of published works that were available in English, and articles related to the consequences and side effects of marijuana use, as well as therapeutic benefits in all settings. We excluded duplicates, abstracts, and non-English articles.

Results and discussion

Marijuana: natural and synthetic (1 Comparative Study, 2 Review Articles, 1 Systematic Review)

One of the most studied organic components in marijuana is Delta-9-tetrahydrocannabinol (THC).⁷ This hormonal compound binds to cannabinoid receptors in the brain that mediate emesis, appetite, and mood, thus terming marijuana as a cannabinoid.⁷ Marijuana is produced in a usable form by shredding marijuana leaves, stems, seeds, and flowers of the *Cannabis sativa* plant, *Cannabis indica* plant, or hybrids.⁸ It can be used by smoking the resulting product via cigarettes, cigars, water pipes, pipes, or blunts, which is marijuana rolled in tobacco leaves. Marijuana can also be consumed orally in baked goods and can be used in tea or used to create oils. Even further, the resin of the flower, called hashish, can also be smoked by users independently, when mixed with tobacco, or can be consumed orally.⁸

In addition to marijuana grown naturally, synthetic cannabinoids can also be produced and consumed to try and simulate the effects of natural marijuana.⁹ Typically, they have been branded as “Cloud 9,” “Spice,” “herbal incense,” “K2,” and “Mojo,” among other names.⁹ Synthetic cannabinoids bind the same receptors as marijuana, but the agonism at cannabinoid receptors by synthetic forms can be unpredictable compared to the known, partial agonism of natural forms.⁹ In fact, synthetic cannabinoids tend to bind to cannabinoid receptors with much higher affinity and efficacy when compared to natural forms.¹⁰ The high potency of these molecules in addition to their psychotropic effects provides an explanation for the illicit use of these substances, as well as greatly increases the risk of acute toxicity.^{9,10} The use of synthetic cannabinoids tends to be more common in younger users, due to the fact that they are easily accessible, inexpensive, and may be difficult to identify with routine drug screening.¹⁰

Both organic and synthetic forms of marijuana aim to mimic the effects of neurotransmitters naturally produced by the human body, which lend purpose to the existence of cannabinoid receptors located in the brain. These compounds have been termed endocannabinoids, or endogenous cannabinoids.⁹ Examples include 2-arachidonylglycerol (2-AG) and N-arachidonoyl ethanolamide (anandamide).⁹

Contamination (2 Review Articles, 1 Letter to the Editor, 1 Book Chapter, 3 Case Study, 1 Case Series, 1 Retrospective Analysis)

In order to appropriately discuss marijuana use, it is important to acknowledge the contaminants that may be found in recreational products that may impact the findings of recreational use-related studies. Many of the microorganisms that are found on herbal marijuana are exclusively plant pathogens and have no cross-infectivity with humans.¹¹ However, there is a subset of opportunistic plant pathogens that are associated with marijuana, such as the spores of *Aspergillus fumigatus* and *Mucor* species, both of which are shown to survive in marijuana smoke.¹¹ Other studies have also suggested possible contamination with *Cryptococcus* spp. as well as bacterial pathogens such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*.¹² Since the use of marijuana is still not legalized across the United States, there is concern over the use of illegal pesticides on marijuana plants. It is reported that the Environmental Protection Agency has not proposed pesticide guidelines because of the illicit status of marijuana use in some states.¹³

As such, clinicians need to recognize and entertain the possibility of contamination and infection in marijuana users and the comorbidities of patients who exhibit infectious symptoms. This is especially important in the immunocompromised population since *A. fumigatus* and *Mucor* species infection can lead to devastating consequences and possibly death in this population.¹⁴ For instance, infection with *Aspergillus* spp. can lead to invasive Aspergillosis in immunocompromised patients such as those who are undergoing chemotherapy or are co-infected with human immunodeficiency virus (HIV).¹⁴ Marijuana smokers who also suffer from frequent asthma attacks as well as those who are diagnosed with cystic fibrosis are also at an increased risk of allergic bronchopulmonary Aspergillosis (ABPA).¹⁴ Immunocompetent individuals with structural damage in their lungs can also be at risk of acquiring chronic pulmonary Aspergillosis.

There have been multiple theories trying to explain the connection between marijuana and *Aspergillus* infection. Some argue that contaminated marijuana might not be the source of infection after all.¹⁵ They explain that the act of smoking not only damages the lung's structures, leading to cavity formation, but it also negatively affects the alveolar macrophages.¹⁵ Together, these effects create a perfect environment for *Aspergillus* spp. to colonize. The priming of this

environment in combination with other patient comorbidities may place some patients at particularly high risk of infection. Future studies are needed to clarify the proportionate causal blame in patients affected by this species.

Similar to reported cases of invasive Aspergillosis in immunocompromised patients, there have been reports of infection with *Mucor* spp. following marijuana use.¹⁶ For instance, a recent case study documented the case of a diabetic patient who passed away after getting diagnosed with pulmonary mucormycosis.¹⁶ Further investigation revealed that he had begun smoking medical marijuana only 3 months before his diagnosis. It was hypothesized that the combination of poorly controlled diabetes and emphysema caused by extensive cigarette smoking made him more susceptible to acquire this fungal infection. They suspected that the source of infection was inhalation of airborne spores as he smoked marijuana.¹⁶

In addition to harboring these infectious agents, it has been shown that *Cannabis* can also accumulate heavy metals in its own tissues even to the extent of making *Cannabis* a viable option for bioremediation.¹³ Although the human body requires a low concentration of heavy metals, at high levels these elements can pose a problem and lead to severe toxicity. There are different ways that marijuana can contain contaminants. Cannabis can store heavy metals in its tissue by absorbing them directly from the soil.¹⁰ Alternatively, this contamination may occur as a result of processing.¹⁰ Finally, to increase the street value of marijuana, these metals might be added intentionally to increase the weight of the product.^{10,17} There have been multiple case studies that documented the consequences of various heavy metal toxicities as a result of smoking marijuana.^{18,19} For instance, one study reported a possible arsenic exposure leading to cannabis arteritis following smoking contaminated marijuana.^{18,19} Cannabis arteritis is a form of thromboangitis obliterans that can potentially lead to serious complications. There have also been multiple cases of lead toxicity among cannabis users. This is mainly due to adulteration and handling of illegal marijuana in order to increase the weight and value of the product.¹⁷

In conclusion, clinicians should keep in mind that the contamination of marijuana with heavy metals, pesticides, and microorganisms may impact the findings of studies related to marijuana use. Figure 1

CB1 and CB2 receptors (6 Review Articles, 7 Original Research Studies)

There are two known types of cannabinoid receptors within the brain, abbreviated as CB1 and CB2. Both receptors are G protein-coupled, that activate adenylyl cyclase and mitogen-activated protein kinase (MAPK) to mediate downstream effects.²⁰ CB1 receptors are also coupled to potassium and calcium channels to mediate a downstream cascade and these receptors can also be found in the peripheral nervous system.²⁰

Both CB1 and CB2 receptors have been found on immune cells, suggesting there are cannabinoid effects on immune functioning, such as the regulation of cytokine release.²⁰ It is through this regulation where much research is underway.

From a non-immunologic standpoint, activation of these G protein-coupled receptors via cannabinoids has shown promising results for the treatment of a variety of central nervous system diseases. For instance, studies in animal models with Alzheimer's Disease have shown that the use of THC not only helped prevent the progression of the neurodegenerative disease, but also restores memory and cognitive functioning.^{21,22} In addition, both observational data and randomized control data have reported that THC has the potential to reduce symptoms of chronic neuropathic pain, cancer related pain, chemotherapy-induced side effects, headaches, Parkinson's Disease, and Multiple Sclerosis.²³

The discovery of the psychotropic effect of THC, as well as the increase in the widespread use of cannabis as a recreational drug in the 1970s, prompted the initiation of extensive research on how this substance affects the brain.²⁴ This ultimately led to the discovery of CB1 and CB2 receptors, as well as recognition of endocannabinoids.²⁵ Because CB2 receptors have been demonstrated to remain mostly in the periphery, the neurobehavioral and psychotropic effects of cannabis is thought to involve activation of CB1 receptors in the cerebral cortex, substantia nigra, hippocampus, globus pallidus, caudate-putamen, and cerebellum.^{20,26} The involvement of this receptor in the ongoing release of different neurotransmitters is hypothesized to be the primary mechanism by which cannabis would alter brain processes, including increasing dopamine release in the nucleus accumbens (NAc) and ventral tegmental area (VTA), the primary reward centers of the brain.²⁵ This is achieved by inhibition of the release of the glutamate onto GABAergic neurons.²⁵

While this mechanism may explain the pleasurable, euphoric sensation exhibited by some, it fails to explain the different behavioral changes that have been reported. While some users experience an extreme sense of pleasure, relaxation, and euphoria, others report anxiety and depression after cannabis use.^{24,25,27} Even within the same user, the effect produced by cannabinoids can be unpredictable and different between each use.²⁸ The differing behavioral changes can be explained by the variable activation of CB2 receptors, which do exist in smaller quantities in the VTA and NAc, between each use and between different individuals.^{29,30,31} In contrary to the CB1 receptor, however, activation of the CB2 receptor leads to aversive behavior by inhibiting the NAc dopamine release and VTA dopaminergic activity.^{29,30,31} Therefore, cannabis can be rewarding or aversive depending on the balance of the downstream effects of these opposing receptors. This also explains why individuals may be more susceptible than others to dependence on cannabis, as the expression of CB1 and CB2 receptors can greatly vary in the brain of different patients.³²

Genetic factors and addiction (3 Original Research Studies, 1 Review Article, 3 Clinical Trials)

The primary psychotropic effects of cannabis are primarily thought to be due to the THC-CB1 interaction. The CB1 receptor is encoded by the Cannabinoid Receptor 1 (CNR1) gene, a gene that is located in the long arm of chromosome 6 at position 15 (6q15).³³ Variation within this gene has been the target of many studies that aim to investigate the relationship between CNR1 polymorphism and cannabis addiction. However, the results of such studies have produced mixed and inconsistent results and have failed to draw a solid conclusion regarding the relationship between CNR1 polymorphism and cannabis dependence. This is largely due to small sample sizes, methodological differences, and more importantly the effect of environmental factors in addiction. For instance, while the study done by Hartman et al.³⁴ in 2009 concluded that there is no association between the single nucleotide polymorphism (SNP) rs806380 and cannabis dependence, an analysis done by Agrawal et al.³⁵ in the same year on rs806380 reported that in fact individuals with this polymorphism are more likely to develop cannabis dependence compared to those with other genotypes. Other studies have also investigated the role of an rs20232239 polymorphism in withdrawal and craving symptoms, and found that certain individuals with this polymorphism are more likely to suffer cannabis withdrawal and craving symptoms compared to those with other genotypes.³⁶

Other genetic causes linked to cannabis dependence are polymorphism of the Fatty Acid Amide Hydrolase (FAAH) gene. FAAH is an enzyme that is responsible for the breakdown and degradation of endocannabinoids.³⁷ This enzyme is encoded by a gene that is located in short arm of chromosome 1 location 33 (1p33).³³ Although the studies investigating the association of FAAH gene polymorphism and cannabis addiction have also shown inconsistent results, polymorphism rs32440 has been implicated in cannabis addiction.³⁸ Due to the involvement of FAAH in cannabis withdrawal and craving, researchers have recently targeted this enzyme for drug development. Recent studies have focused on increasing the concentration of endocannabinoids via FAAH-inhibitors in order to help reduce cannabis withdrawal symptoms, relapse, and craving.

Withdrawal (2 Review Articles, 1 Original Research Study)

Symptoms of marijuana withdrawal include sleep disturbance, anger, restlessness, irritability and anxiety, appetite changes and weight loss, and tremor.³⁹ The time of onset of these withdrawal symptoms is similar to other substances of abuse, such as tobacco and alcohol. Symptoms commonly begin within 24–48 h following abstinence and continue for 1–2 weeks.^{40,41} As many as 35%–75% of individuals with cannabis dependence reported experiencing such symptoms.³⁹ The United

States Food and Drug Administration (FDA) has not approved any medication to treat withdrawal symptoms. However, multiple existing medications such as zolpidem, buspirone, and gabapentin are being actively investigated.

GI side effects Intractable vomiting—cannabinoid hyperemesis syndrome

(1 Systematic Review, 1 Clinical Trial, 10 Review Articles, 10 Case Reports, 2 Case series, 1 Original Research Study)

The main gastrointestinal effect of chronic marijuana use is intensive vomiting, as described in a systematic review of systematic reviews by Campeny et al.⁴² This syndrome has been referred to as cannabinoid hyperemesis (also called cannabinoid hyperemesis syndrome, or CHS). Cannabinoid hyperemesis was first reported in the literature in 2004 and most reported incidents of this syndrome were in males who began using cannabis daily as teenagers, and subsequently developed symptoms after years of daily cannabis use.^{43,44}

Pathophysiology

The complete pathophysiology of cannabis-induced vomiting is not fully understood. It is hypothesized that CB1 receptors are found in the gastrointestinal tract, specifically the enteric plexus, and their activation induces vomiting.⁴⁵ Stimulation of these receptors is theorized to slow gastric peristalsis and emptying in a dose-dependent manner.⁴⁶ Another theory is that cannabinoid receptors interact with the hypothalamic-pituitary-adrenal (HPA) axis, and respond to stimulation causing increases in corticotropin-releasing hormone levels that cause vomiting.⁴⁷ Therefore, those with sympathetic stimulation, from high levels of mental stress for example, may be more likely to develop vomiting when chronically smoking marijuana. Both leading pathophysiologic explanations for vomiting, however, involve alterations in thermoregulation. It is also hypothesized that cannabis toxicity alters hypothalamic thermoregulation, which is responsible for the common observation of compulsive hot bathing to relieve symptoms of vomiting.⁴⁸ Finally, marijuana contaminants over a chronic period of time leading to toxicity, which may lead to vomiting, cannot be ruled out as a pathophysiologic cause.

Clinical presentation

The classic sequence of vomiting symptoms are characterized by initial abdominal discomfort and nausea followed by vomiting, thirst, and polydipsia.⁴⁹ It is important to note that vomiting without abdominal pain should rule out CHS as a potential diagnosis, as abdominal pain is a hallmark symptom.⁴⁹ It most commonly presents in patients who *chronically and heavily* use cannabis daily for many years, rather than those who use

marijuana intermittently or socially.⁵⁰ However, extended bouts of profuse, uncontrollable vomiting, with nausea that lasts up to several hours, also warrants investigation into marijuana misuse.⁵¹ Typically, hypovolemia results due to the intense vomiting, with patients presenting with possible tachycardia, orthostatic hypotension, and elevated creatinine that may be reversible upon administration of appropriate treatment. Weight loss has also been reported with some patients reporting up to 15 kg over a period of 5 years.⁵²

Diagnosis

When evaluating patients, the differential diagnosis should include cannabis withdrawal, gastroenteritis, hepatobiliary disease, hyperemesis gravidarum, bulimia, Addison Disease, and migraine headaches.^{43,44,52,53} Most importantly, the differential diagnosis should include Cyclic Vomiting Syndrome, of which many symptoms overlap with Cannabinoid Hyperemesis Syndrome. The diagnosis for cannabinoid-induced vomiting is largely clinical, though, and should include investigating the history for cannabis use, episodes of uncontrollable vomiting over the course of several months, severe nausea, and the cessation of symptoms with cessation of cannabis use.⁴⁷ Patients who regularly draw compulsive hot baths for themselves to relieve the abdominal discomfort, nausea, and vomiting can also help to narrow the diagnosis.⁴⁴

Cyclic Vomiting Syndrome and Cannabinoid Hyperemesis Syndrome, while having many similar symptoms, should be distinguished in a clinical setting. Cyclic Vomiting Syndrome patients are characterized by recurrent episodes of heavy nausea, vomiting, and abdominal pain similar to Cannabinoid Hyperemesis Syndrome.⁵⁴ Cyclic Vomiting Syndrome patients may have a history of migraines, psychiatric comorbidities, and often experience rapid gastric emptying.⁵⁴ Use of marijuana and dronabinol can also be triggers for Cyclical Vomiting Syndrome, of which the treatment consists of cessation of marijuana and avoidance of marijuana-related triggers.⁵ However, the difference between Cannabinoid Hyperemesis Syndrome and Cyclical Vomiting Syndrome patients is that Cannabinoid Hyperemesis Syndrome patients have largely absent comorbidities except for a history of chronic marijuana use, cure after cannabis cessation, and have delayed gastric emptying as opposed to rapid gastric emptying.^{54,55} The delay in gastric emptying is well established via studies with the approved synthetic cannabinoid agent, dronabinol. Dronabinol has been shown to delay gastric emptying of solids, delay colonic transit and propulsive activity, and cause loss of colonic tone via cannabinoid binding of CB1 receptors in myenteric nerve fibers.^{56,57}

Treatment

The current goal of treatment is focused on marijuana and cannabis cessation with concurrent symptom control.⁵⁸

Hot water bathing and showering is a learned behavior that patients often find for nausea relief due to extrinsic rebalancing of body temperature.⁵⁹ However, the hot water may also induce enteric blood flow outward toward the periphery, leading to less stimulation of the cannabinoid receptors in the gastrointestinal system, namely the gut, and a reduction of symptoms in the patient.⁶⁰ This mechanism has been named as cutaneous steal syndrome.⁶⁰

Other symptom control measures focus around rehydration and antiemetics.⁵¹ However, it is important to note that patients may not have relief with the administration of antiemetics.⁵² Benzodiazepines can be considered as a short term treatment for patients post-hospitalization if the patient expresses serious intent to cease cannabis use.⁴⁹ Haloperidol administration, either orally or intravenously, has also been reported to help cannabinoid-induced vomiting, due to the ability to block postsynaptic dopamine receptors and subsequent inhibition of the medulla.^{61,62} Finally, capsaicin-based creams have been reported to reduce the symptoms of vomiting and nausea without a systemic mechanism of action.⁶³ Ultimately, long-term relief of symptoms is achieved through abstinence, with the re-onset of symptoms commonly observed if cannabis is resumed suggesting a lack of sensitization normalization by cannabinoid receptors over time.⁵⁰

While marijuana is a known antiemetic, especially for the treatment of nausea and vomiting in chemotherapy-treated cancer patients, there is a hypothesis that over stimulation with marijuana gives an undesired pro-emetic effect.^{64,65} The antiemetic effect is presumed to be due to downregulation of GABAA brainstem sites leading to suppression of nausea and vomiting.⁶⁵ However, chronic GABAA inhibition in the brainstem endocannabinoid sites may result in unimpaired sympathetic activity leading to the pro-emetic effects seen in cyclical vomiting syndrome and cannabinoid hyperemesis syndrome.⁶⁵ Therefore, cessation is imperative when pro-emetic effects are evident.

Hepatotoxicity

(2 Original Research Studies, 4 Review Articles, 2 Case Reports)

Hepatotoxicity is a potential complication of illicit drug usage, including marijuana.⁶⁶ In fact, a study by Borini et al.⁶⁶ evaluating clinical and laboratory alterations in chronic marijuana users demonstrated that hepatomegaly, splenomegaly, and hepatosplenomegaly were detected in 57.7%, 73.1%, and 46.2% of patients using marijuana alone (total sample n=26). In addition, 20 out of 26 patients demonstrated evidence of transaminitis.⁶⁶ In this section, we describe the pathophysiology, clinical presentation, diagnosis, and treatment of cannabis-induced hepatotoxicity.

Pathophysiology

After introduction of THC into the body, it is absorbed into the systemic circulation, hydroxylated in the liver and lungs, and broken down into inactive metabolites in the liver.⁶⁶ Studies have shown a stark upregulation of Acetyl Coenzyme A Carboxylase and Fatty Acid Synthase, with inhibition of Carnitine Palmitoyl Transferase upon exposure to exogenous THC; the process shifting the balance in favor of lipogenesis over fatty acid oxidation and depleting cellular Adenosine triphosphate (ATP) which can lead to hepatocyte injury.⁶⁷ Other studies have showed that mice who were administered cannabidiol resulted in an increase in hepatic enzymes, such as Cytochrome P-450 2e1, Cytochrome P-450 2b10, uridine diphosphate glucuronyltransferase, and oxidized glutathione.⁶⁸ Therefore, acute toxicity of cannabis or the synthetic compounds, combined with endogenous cannabinoids, can result in acute liver injury.

Clinical presentation

In addition to jaundice, abdominal pain, and abdominal fullness associated with acute liver injury, patients can also present with signs of metabolic derangement related to obesity and insulin resistance, which are modulated by CB2 receptor activation.⁶⁹ Patients have also been observed to present with hypokalemia, rhabdomyolysis, acute kidney injury, and the aforementioned insulin resistance, which has triggered the search for CB2 receptor antagonists as therapeutic agents.⁷⁰ Marijuana has been linked to activating CB2 receptors in the liver resulting in liver fibrosis, eventual cirrhosis, and possibly hepatocellular carcinoma.⁷¹ Despite these occurrences, cross-sectional studies have demonstrated that the largest percentage of patients present with a classic picture of acute hepatitis.⁶⁶

Diagnosis

Cannabis-induced liver injury is a diagnosis of exclusion in patients who are symptomatic with a known history of cannabis abuse. Clinicians should seek out evidence of transaminitis, elevated gamma glutamyl transpeptidase (GGT), and elevated bilirubin. Clinicians should also look to rule out causes like acetaminophen ingestion, alcohol intoxication, and viral infections.⁷² In a study on chronic marijuana abusers, 25% of the liver biopsies were consistent with degenerative changes which may lend some credibility to conformational biopsy in chronic users.⁷³

Treatment

Treatment of hepatotoxicity should center around counseling patients on cessation of marijuana abuse. N-Acetylcysteine (NAC) has been found to be hepatoprotective as it replenishes the supply of reduced glutathione and displays antioxidant properties, which slow the progression of liver injury.⁷¹

There is also an ongoing search for CB1 receptor antagonists that display selectivity for the liver, which may slow the progression of liver injury and fibrosis.⁶⁷ The remaining treatment should revolve around supportive care until evidence of acute liver injury has resolved. Furthermore, as the pathogenesis of cannabis-induced hepatotoxicity becomes more elaborate and well-defined, new medications can be discovered with the intent to treat or cure.

Pancreatitis (1 Systematic Review, 2 Case Reports, 3 Original Research Studies, 1 Case Series, 1 Review Article)

The first case of *cannabis-induced pancreatitis* was reported in 2004.⁷⁴ Since then, more cases have been reported and literature published elaborating the proposed mechanism of action. In this section, we discuss the pathophysiology, clinical presentation, diagnosis, and treatment of cannabis-induced pancreatitis.

Pathophysiology

The first case of *cannabis-induced pancreatitis* was reported in 2004.⁷⁴ Since then, more cases have been reported and literature published elaborating the proposed mechanism of action. It has been established that CB1 and CB2 receptors are found in the Islets of Langerhans cells in the pancreas.⁷⁵ In mice, the endogenous cannabinoid Anandamide has been proposed as one of the mediators of necrotizing pancreatitis.⁷⁶ Studies conducted on mice have shown worsening pancreatic edema and inflammation consistent with a rise in serological markers after anandamide administration; these markers include lipase, amylase, pro-inflammatory interleukin-1 beta, and poly-C-ribonuclease.⁷⁷ With the assumption that exogenous cannabis products mimic endocannabinoids, research is ongoing to determine if cannabis products also activate CB1 and CB2 receptors in humans, which would link misuse to pancreatitis symptoms.

Clinical presentation

In 2017, Barkin et al.⁷⁸ published the mean age of acute pancreatitis from cannabis misuse as 26.3 years of age. In patients with significant marijuana use, the classical signs and symptoms of acute pancreatitis from cannabis mimic pancreatitis from other causes and include epigastric abdominal pain, nausea and vomiting.⁷⁹

Diagnosis

Pancreatitis from cannabis use is a diagnosis of exclusion, and clinicians should be first be able to rule out other causes like gallstones pancreatitis, alcohol-induced pancreatitis, other drug causes, and infections.⁷⁴ According to the Revised

Atlanta Classification, patients with acute pancreatitis should have two of the following three findings: epigastric pain radiating to the back, lipase and amylase levels three times the upper limit of normal, and imaging evidence by computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US).⁸⁰ There is no additional criteria for the diagnosis of marijuana induced pancreatitis. Furthermore, the Bedside Index for Severity in Acute Pancreatitis (BISAP) along with other severity scores can be used as valuable tools to predict mortality in acute pancreatitis due to cannabis toxicity.⁸¹

Treatment

Similar to other side effects previously discussed, it is important to center treatment around cessation of cannabis.⁷⁸ Furthermore, supportive treatment for the diagnosed pancreatitis mimics standard pancreatitis protocols with pain management, bowel rest, and intravenous hydration. AM 251, a CB1 receptor antagonist, has promising potential to decrease the progression of necrotizing pancreatitis improving the overall survival rate, based on the results in a rat model.⁷⁶ But till date no drug has been approved for the use of marijuana-induced pancreatitis.

Cardiovascular effects (1 Systematic Review, 1 Clinical Trial, 3 Review Articles, 1 Original Research Study)

The most common cardiovascular side effect of acute marijuana toxicity is increased heart rate and blood pressure.⁸² Increases in heart rate have been established to be dose-dependent.⁸³ While significant raises in both systolic and diastolic blood pressure were reported in doses of marijuana of just 10mg, blood pressure changes seem to be secondary to elevated heart rate rather than the dose of marijuana.⁸⁴ Over time, chronic marijuana use produces a decreased heart rate and subsequent drop in blood pressure (with some even reporting orthostatic hypotension as a result).^{82,85} Repeated exposure to marijuana has also been found to diminish valsalva maneuver responses, which is consistent with centrally mediated reduced sympathetic activity and increased parasympathetic activity.⁸⁵

Other acute cardiovascular events that have been reported include myocardial infarction, cardiomyopathy, stroke, arrhythmias, and cardiac arrest.^{42,86} Weight gain with fluid retention and plasma volume expansion has also been reported, though the plasma volume expansion may be a compensatory for orthostatic hypotension symptoms mentioned above.⁸² Minimal electrocardiogram changes are noted in patients using marijuana, but there have been premature ventricular contractions reported.⁸⁴

The mechanism for cannabis-mediated cardiovascular effects is hypothesized to be caused by THC effects on the autonomic nervous system, specifically by activation of the CB1 receptor.^{83,86} With acute use, THC produces sympathetic

excitation. But with prolonged administration, inhibition of the sympathetic nervous system results.⁸²

Neurologic effects (2 Systematic Reviews, 3 Review Articles, 3 Original Research Articles, 8 Clinical Trials)

According to Chye et al.,⁸⁷ one of the many findings of chronic cannabis use included neuroimaging that resulted in smaller hippocampal volume when compared to control groups and less frequent cannabis users. A subsequent study showed the hippocampus of 14 heavy cannabis adult users following 6.7 months of supervised abstinence; the results showed hippocampal atrophy persists and imparts long-term structural and functional damage.⁸⁸ Another study focusing on the long-term effect of chronic cannabis use in adolescents also supported this finding, and even observed that earlier life usage results in exacerbation of age-related cognitive dysfunction.⁸⁹

With regards to the nucleus accumbens, chronic marijuana use has shown increased gray matter density and volume.^{90,91} On the contrary, the results of neuroimaging studies on the amygdala and striatum have shown a great degree of inconsistency. For instance, while some studies reported an increase in the gray matter density of the amygdala and striatum in cannabis users, others have shown no differences in gray matter volume changes between the control group and cannabis users.^{92,93} The result of such studies has been further complicated since the discrepancies seen in the gray matter densities may have already been present in the individuals prior to cannabis use. This poses a question of whether these structural differences are a vulnerability factor for cannabis dependence as opposed to being caused by cannabis itself. The result of neuroimaging studies on cerebellum and the pre-frontal cortex (PFC) are somewhat limited and conflicting as well. The most consistent finding regarding changes in the cerebellum is alteration in cerebellar structure and function, as well as an increase in cerebellar gray matter volume.⁹⁴ In contrast to the cerebellum, cannabis users were found to have a smaller volume of PFC compared to control groups. More specifically this reduction has been reported in the orbitofrontal cortex (OFC).⁹⁵ Studies focusing on the thickness of the cortices also found a negative correlation between the cortical thickness and age of onset, such that early cannabis use was associated with thicker PFC.^{96,97}

Functional MRIs have been paired with cognitive testing in order to investigate the effect of cannabis use on brain activities.⁹⁸ Although the results have varied due to different study parameters, amount and duration of cannabis use, and subject's individual differences, most studies reported deficits in working memory, decision-making, and processing.⁹⁸ In addition, acute cannabis administration has been associated with increased risk-taking behavior in both infrequent and frequent users.⁸² This is a dose-dependent effect, meaning that only high enough doses of cannabis that produce intoxication can lead to such degrees of disinhibition.⁹⁹ The most consistent

finding, regarding the chronic effect of cannabis abuse, has been its detrimental effect on verbal learning and memory.¹⁰⁰ Multiple well-controlled studies have showed that the abilities to encode, recall, and recognize were progressively worsened with increasing years of marijuana use. Other factors such as frequency, dose, and age of onset of cannabis use were also involved in the degree of impairment.¹⁰⁰ Finally, the most common neurologic side effects reported in patients using medical marijuana include dizziness and relapse of multiple sclerosis.⁴² Patients using marijuana recreationally have also been noted to suffer from sleep disturbances, likely due to interruptions in slow wave sleep.⁴²

Pulmonary effects (3 Systematic Reviews, 1 Original Research Study)

Short-term marijuana exposure produces bronchodilation.¹⁰¹ The pathophysiologic relationship between long-term marijuana smoking and airflow obstruction is still unknown. However, it has been established that regular cannabis use is associated with a greater risk of asthma, COPD, and pneumonia.¹⁰² It is important to note that lack of concomitant tobacco use does not reduce the risk of asthma, COPD, and pneumonia in marijuana users.¹⁰² It is also important to note that tobacco users have the highest prevalence of respiratory disease regardless of marijuana use.¹⁰² A systematic review of systematic reviews performed in 2020 has found there to be an increased risk of lung cancer in inhalational marijuana users, ranging from 8% to 410% after controlling for confounding factors.⁴² They also found that patients who use marijuana moderately or heavily are more likely to suffer from cough, increased sputum production, wheezing, or dyspnea.⁴² This is in contrast to conclusions made by the National Academy of Sciences, Engineering, and Medicine who concluded that based on their summary of systematic reviews in 2017 that there is moderate evidence of no statistical association between cannabis smoking and the incidence of lung cancer.¹⁰ Further studies are needed to delineate the effects of marijuana use and the incidence of lung cancer.

Therapeutic use of marijuana

Marijuana has long been used as a medicinal plant. In 1985, pharmaceutical companies received approval to begin developing $\Delta 9$ – THC preparations (dronabinol and nabilone) for therapeutic use.¹⁰ Since this time, over 33 states have approved of the use of marijuana for medical purposes.² Here, we discuss several of the purported therapeutic benefits of medicinal marijuana.

Antiemetic effects (1 Systematic Review, 1 Review Article, 1 Original Research Study)

Cannabis has long been recognized to have medical benefits when it comes to blocking both acute and delayed emesis. This

is due to interaction of this chemical with the CB1 receptors.⁶⁴ Currently, Dronabinol, a synthetic form of THC, has been used as an antiemetic agent and an appetite stimulant.¹⁰ This is especially effective in controlling the nausea and vomiting post-chemotherapy in cancer patients.¹⁰ Multiple studies have shown that oral administration of $\Delta 9$ – THC was shown to significantly reduce the nausea and vomiting of cancer patients compared to the subjects in the placebo group.¹⁰ In comparison to D2 receptor antagonist, research has shown that $\Delta 9$ – THC is at least as effective, if not better at suppressing nausea and vomiting.¹⁰³ In a summary of systematic reviews by the National Academies of Sciences, Engineering, and Medicine, it was concluded that there is strong evidence surrounding the use of oral cannabinoids for the treatment of chemotherapy-induced nausea and vomiting.¹⁰ Despite the effectiveness of cannabis as an antiemetic, this substance is still not used as a first line therapy due to its side effects, many of which have been discussed in this manuscript.

Functional chest pain (2 Clinical Trial, 1 Original Research Study)

Noncardiac chest pain can be caused by a variety of conditions, namely gastroesophageal reflux, esophageal mechanical abnormalities, and functional chest pain due to esophageal hypersensitivity. It has been proposed that esophageal hypersensitivity is due to central and or peripheral mechanisms.¹⁰⁴ For instance, it has been hypothesized that sensitization of esophageal sensory afferent neurons leads to heightened perception of visceral stimuli, independently of the intensity of the actual physiological or pathological stimuli.¹⁰⁴ Similarly, sensitization of the central nervous system, either at the brain level or the dorsal horn of the spinal cord can lead to similar consequences.¹⁰³

Currently the treatment of chest pain related to esophageal hypersensitivity only improves the symptoms in 40%–50% of people.¹⁰⁵ Given that the CB1 receptors are located in abundance in the esophageal epithelium, the effectiveness of cannabis as a potential therapeutic agent was studied. This was based on the fact that stimulation of CB1 receptors at this location leads to reduced excitatory enteric transmission and ultimately reduces the hypersensitivity of the esophagus.¹⁰⁵ During a prospective study done by Schey et al., the pain threshold, frequency, and intensity of functional chest pain was compared among a group of patients who received 5mg of dronabinol twice daily and placebo. The result showed a significant increase in the pain threshold and reduced pain intensity and odynophagia among patients who received Dronabinol compared to placebo.¹⁰⁵

Metabolic effects (1 Review Article, 1 Original Research Study)

In reviews of cross-sectional data, it has been shown that cannabis has had protective effects on certain metabolic

processes. In animal models, cannabis is protective against type 1 diabetes. However, the efficacy of this in human trials has not been made evident. This lack of human response may be due to the lack of effect on a molecular level or due to contextual or patient-related factors.¹⁰⁶ Research has also pointed to the non-harmful effects of cannabis on metabolic processes through liver-related studies. Liver function, as measured by liver function tests (LFT, namely transaminases and bilirubin) was shown to be unaffected in relatively healthy people who were not nicotine dependent. Ultimately, LFTs did not significantly rise or fall with elevated cannabis metabolites, which were monitored to approximate the duration of cannabis use and as objective markers.¹⁰⁷ The lack of effects on certain metabolic processes and the potentially protective effects of cannabis use are important to be mindful of in holistic discussions of cannabis use.

Gastroparesis (1 Review Article, 1 Clinical Trial)

Patients with gastroparesis often suffer from symptoms of nausea, vomiting, anorexia, early satiety, and pre-prandial fullness.¹⁰⁸ These patients are most commonly older with comorbidities that are associated with gastroparesis such as neurocognitive disorders, cancer after chemotherapy use, or diabetes.¹⁰⁸ Current treatment includes dietary modifications, prokinetic and antiemetic agents, gastric electrical stimulators, and surgical treatments.¹⁰⁸ THC and CBD, both the active ingredient of cannabis, are known to affect the gut function peripherally and centrally and can regulate the gut motility properties and visceral sensation.¹⁰⁹ Currently, Dronabinol, the synthetic form of THC, has been approved for gastroparesis to aid with nausea, vomiting, and anorexia as an intermittent solution to gastroparesis when other measures to stimulate appetite have not helped. In a study done by Parkman and colleagues the prevalence of use and patient's perceived benefit of marijuana in relieving their gastroparesis symptoms was assessed.¹⁰⁹ The authors concluded that approximately 12% of patients in this category use marijuana for treatment of their symptoms. Within this group patients with more severe symptoms were more likely to use marijuana and perceive it as effective in alleviating their symptoms.¹⁰⁹ It should be importantly distinguished that intermittent use of marijuana for appetite stimulation differs from the chronic daily and heavy committed use of marijuana that leads to CHS, where users often begin in their high school and college years rather than older patients beginning use when comorbidity complications arise.

Limitations

There are limitations to the current review. First, this article was written as an overview of the side-effects of marijuana use in the context of ongoing legalization and liberalization efforts in the United States. As such, some of the topics here within have been presented as a primer for physicians who

may encounter these patients in their practice. At the beginning of each section, we have provided a count of which articles including systematic reviews, clinical trials, case series, or case reports were included pertaining to each topic discussed. We would encourage physicians to use these articles in addition to reviewing other pertinent literature to expand their knowledge further. In addition, this article was written as a narrative review and as such lacks the power of a systematic review for summarizing all of the available literature with statistical significance. We have, however, attempted to provide readers with a comprehensive overview of several of the known organ-system based consequences regarding marijuana use in order to familiarize physicians with these side effects moving forward.

Conclusion

This manuscript represents a comprehensive review of cannabis-induced vomiting, hepatotoxicity, pancreatitis, and extra-gastrointestinal side effects. There is a demonstrated need for future research to elaborate and solidify the pathophysiology behind these side-effects, in addition to research on the effectiveness of new medications on the treatment and prevention of these symptoms. It should be noted that legalization of marijuana occurred in 14 states in 2019, and many THC related side-effects could take years to manifest after legalization, unless the chronic and heavy use of marijuana began before legalization. Therefore, physicians, particularly emergency physicians, should be aware and vigilant in history taking to a patient's marijuana use, so that the side effects of marijuana are not missed on an initial presentation to the emergency room. Physicians should also be aware that patients may need long-term support to prevent the recurrence of abdominal pain and vomiting, so medications, such as tricyclic antidepressants, can be started at this time and titrated up accordingly along with benzodiazepines for intermittent anxiety support while attempting to cease marijuana. Finally, counseling and psychotherapy may be necessary in some instances to help with cessation of marijuana in order to mitigate the side-effects discussed above.

Author contributions

Asim Kichloo, Michael Albosta, and Michael Aljadah are credited with substantial contribution to the design of the work, literature review of all the sections discussed, the revision of critically important intellectual content, final approval of the published version, and agreement of accountability for all aspects of the work. Zain El-Amir and Ghazaleh Goldar are credited with substantial acquisition, analysis, and extraction of the literature reviewed for the manuscript, drafting the manuscript, final approval of the version to be published, and agreement of accountability for all aspects of the work. Muhammed Zatmar Khan is credited with significant contribution to the design of the manuscript and interpretation of the data, the revision of critically important intellectual content, final approval of the version to be published, and agreement of accountability for all aspects of the work. Farah Wani, Dushyant Singh

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Data availability

The data supporting this narrative review are from previously reported studies and data sets, which have been cited here within.

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