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Medical Consequences of Marijuana Use: A Review of Current Literature

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Abstract With the advent of legalization of marijuana for medicinal and recreational purposes, and the increase use of marijuana, healthcare providers will be increasingly confronted with marijuana users as patients in clinical environments. While there is vast literature regarding the societal and mental health harms associated with marijuana use, there is a paucity of reviews of the potential consequences of marijuana use on physical health or medical conditions. We examine the recent literature on the physical harms associated with illicit and legal marijuana administration. We surveyed the peer-reviewed medical literature from 1998 to 2013 of studies assessing the association of marijuana use and physical diseases. We conclude that healthcare providers should be cognizant that the existing literature suggests that marijuana use can cause physical harm. However, evidence is needed, and further research should be considered, to prove causal associations of marijuana with many physical health conditions.

Keywords Marijuana · Medical consequences · Review · Substance use and related disorders · Psychiatry

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Introduction

The legal and illicit use of marijuana is increasing. In the USA, 16 states have legalized marijuana use for medical purposes, with more currently considering some form of legalization for medical or non-medical use [1]. This legislative trend runs counter to US law, which still prohibits the production, sale, procurement, and use of marijuana independent of purpose. Marijuana has been designated a Scheduled I medication by the US Drug Enforcement Agency, indicating that marijuana is among "the most dangerous class of drugs with a high potential for abuse and potentially severe psychological and/or physical dependence" [2], although the rationale for this assessment has been controversial [3–6]. Recently, the American Psychiatric Association's revised *Diagnostic and Statistical Manual of Mental Disorders* affirmed that marijuana use can progress to a diagnosis of marijuana use disorder, a condition requiring treatment [7].

Cannabis is the world's most widely used illicit substance. In 2010, as much as 5 % of the world's population had used marijuana [8]. In 2012, more than 100 million people in the USA (42 % of the population) had ever used marijuana and more than 30 million (12 %) had used marijuana in the previous year [9]. Use by underage populations within the USA has risen over the last ten years [10]. Marijuana use is particularly high among youth and young adults: 23 % of high school students have used in the previous month [11], 40 % of high school seniors have ever used marijuana [10], and 56 % of young adults had used marijuana in their lifetime [10]. The incidence of marijuana use disorder is increasing [12, 13]. With the advent of legalization of marijuana use for medicinal and recreational purposes, and the increase in prevalence of marijuana use disorder, healthcare providers will be increasingly confronted with marijuana users as patients in their clinical environments. Addressing the potential medical harms of recreational, incidental, and pathologic marijuana

use will be more important as increasing numbers of these patients access healthcare environments.

While much is known about the psychological, legal, and societal effects of marijuana, less is known about how marijuana affects body systems and incites acute or chronic physical or medical harms. In addition, because the use of medical marijuana is not approved by the US Food Drug Administration, practitioners have little reference to the side effects that result from marijuana's medicinal application. Paradoxically, practitioners need for more information regarding potential side effects, medication interactions, and medical and mental health morbidity is precluded by its recognition as a Schedule I drug by the USA. Orally-administered medications that use marijuana constituents (e.g., Sativex), contain synthetic products found in marijuana (e.g., dronabinol), and/or contain chemicals similar to marijuana (e.g., nabilone) are approved in various countries. However, these derivative medications offer little insight into the potential physical harms of recreational, medicinal, or illicit inhaled marijuana.

We have previously reviewed the latest literature regarding association of marijuana and physical illness [14]. In addition, several reviews of the medical consequences of marijuana use have concentrated on the mental health, societal, and environmental harms of the substance [12, 15–18]. Recent increases in medicinal, recreational, and pathologic marijuana use, as well as emerging literature, require a critical re-evaluation of the medical harms of marijuana.

In this review, we examined the recent peer-reviewed literature (MEDLINE and PubMed from 1998 to August 2013) to identify, review, and report on potential medical harms of marijuana. We concentrated this review on the *medical consequences* associated with the administration of marijuana. We reviewed recent peer-reviewed literature that indicates a possible association between marijuana use and physical health conditions, grouped by body systems, including immunologic, neoplastic, respiratory, cardiovascular, neurologic, renal and urologic, gastrointestinal, gynecologic, and metabolic. We also review marijuana effects on human physiology and speculate about future research needed to explore the medical harms associated with marijuana administration.

We did not review, in part because the literature is already well reviewed, published work regarding harms associated with such activities of procurement (e.g., legal problems, criminality); physical complications due to use (e.g., trauma due to blunted sensorium); risky practices when using (e.g., risky sexual behaviors); problems in pregnancy, including development of the embryo/fetus (e.g., neurological disorders) [19–24]; or increases or incidence of mental disorders or disease (e.g., psychosis) [25]. We also did not review the concerns of adherence to medicinal treatment, including medication adherence, in persons who use marijuana.

Marijuana Physiology

Marijuana is a heterogeneous and diverse product when procured both legally and illicitly. Marijuana contains bioactive substances that can produce presumptive and realized pathological responses and diseases in humans. Three classes of cannabinoids are known: the phytocannabinoids (PC) from *Cannabis sativa*; the endocannabinoids that are endogenous in mammals and other animals; and the synthetic cannabinoids. The physiologic chemicals in marijuana are PC from *C. sativa*. More than 60 cannabinoids have been identified in marijuana; however, the three most abundant and most often studied are tetrahydrocannabinol (THC), cannabindiol (CBD), and cannabinol (CBN). THC is the psychoactive PC and is a partial agonist for CB1 and CB2 receptors. CBD has no psychotropic effects. CBN is a degradation product of THC and has a mild psychotropic effect. In humans, the CB1 receptors are primarily found in the central nervous system (CNS) and the CB2 receptors are primarily found in peripheral tissue, including cells involved in inflammation and immunity.

The endocannabinoids include arachidonyl ethanolamide; 2-arachidonyl glycerol, n-arachidonyl-dopamine, and virodhamine. A fifth possible endocannabinoid is 2-arachidonyl glycerol ether. The endocannabinoids are intercellular messengers derived from arachidonic acid. As lipophilic compounds, they are integral to the cell membrane and found in the central and peripheral nervous systems, and other body tissue, where they interact with endogenous cannabinoid receptors (CB1 and CB2) and other receptors. Although the functions of the endocannabinoids are not entirely elucidated, the endocannabinoids seem to have important functions including fetal development and the immune system. Several endocannabinoid–receptor systems have been described and, besides CB1 and CB2 receptors, other atypical receptors have been found that bind with various cannabinoid compounds.

Infectious Disease Risk

Owing to potential immune dysfunction, marijuana use may increase risk of a variety of infectious agents. Marijuana decreases immune cell activity, suggesting that use of marijuana can lead to an increased susceptibility to a wide-range of infections [26]. The role of cannabinoids in suppressing the inflammatory response and immunity may also decrease resistance to various infectious agents [27]. For example, two case studies described outbreaks of tuberculosis (TB) in marijuana users [28, 29]. One case study followed 11 youths smoking marijuana in a closed car and contracting the same TB isolate. Interestingly, 14 of their friends also tested positive for TB, suggesting that TB can be transmitted more readily in socially-linked marijuana users

[29]. The risk of TB transmission can be potentially as high as two-fold in marijuana users [28].

Social networks combined with impaired immune function among marijuana users may also have had a role in an outbreak of *Neisseria meningitides*, where both the users and the contacts were linked to marijuana use [30, 31]. Sexually-transmitted diseases are also associated with marijuana use, although it is unclear whether the risky sexual practices and/or impaired immune function may primarily be contributory [32]. Co-users of marijuana, methaqualone, and tobacco users had a higher prevalence and density of oral candida than non-smokers [33, 34].

Marijuana users' risk of developing severe steatosis (fatty degeneration) and fibrosis in the liver through infectious virus vectors has been evaluated. For example, in a sample of 315 patients with untreated chronic hepatitis C who underwent liver biopsy, one study found that marked hepatic steatosis was (1) associated with daily marijuana use; (2) more often seen in daily marijuana users than occasional users; and (3) more often seen in daily users compared with non-users even when hepatitis C genotype and alcohol use was considered [35]. Researchers in another study found that after adjustment for other factors like alcohol use, daily marijuana use was associated with moderate-to-severe fibrosis in patients with chronic hepatitis C [36].

In summary, a few studies explore the relationship between infections and marijuana use outside of risky behaviors associated with marijuana use. Compared with the general population, marijuana users may be more prone to viral and some bacterial infections, including TB. Based on research regarding the harm of marijuana use in patients with chronic hepatitis C, its use in these patients may be deleterious.

Cancer Disease Risk

Marijuana could be potentially carcinogenic. Cannabinoids have been shown to suppress immune function and increase tumorigenic reactive oxygen species, and marijuana tar contains carcinogens similar to the tar in cigarettes [37]. Unfortunately, methodological limitations in many of the reviewed studies, including selection bias, small sample size, limited generalizability, and lack of adjustment for tobacco smoking, may limit the ability to attribute cancer risk solely to marijuana use [37, 38]. In addition, as pre-malignant changes and cancer development may take some time to develop and marijuana exposure tends to occur in youth and young adults, studies may not have enough follow-up time to explore marijuana's carcinogenic risk. In one review, marijuana smoking was associated with changes in alveolar macrophage and bronchial mucosal function but when adjusted for tobacco use the studies did not show a significant association between marijuana use and lung cancer [39]. There have been series of literature reviews associated with marijuana smoking and cancer [39, 40].

Recently, in another review, two cohort studies and 14 case-controlled studies were described [38]. The cohort studies explored the association between marijuana use and adult-onset gliomas, lung, colorectal, prostate, and cervical cancer. Many of the studies had conflicting results or lacked a statistically significant association between marijuana use and cancer. The review points out some limitations of the studies, including possible under-reporting of self-marijuana use, small sample size, and confounders, such as concurrent tobacco smoking. In a case–control study from 1999, 173 patients with squamous cell cancer (SCC) of the head and neck along with 176 cancer-free participants were examined, and investigators found that marijuana smokers had an increased risk for cancer than non-smokers [41]. Interaction effects were found with marijuana use and cigarette smoke, mutagen sensitivity, and use of alcohol. In a recent, large population-based case-controlled study, with adjustments for sex, education, birth year, alcohol use, and cigarette use, there was no significant association between oral cancer risk and marijuana use [42].

There seems to be an association in the literature with marijuana use and bladder cancer [43]. In a case–control study of a convenience sample of men diagnosed with transitional cell bladder cancer involving age-matched controls with no history of cancer, a statistical difference in cancer occurred with those persons who were habitual marijuana users, including associations of marijuana use and stage, grade, and recurrence of the cancer [44]. Several recent studies suggest an association between marijuana use and testicular germ cell tumors [45–47].

Considering the route of exposure to inhaled marijuana, risk for cancers of the head, neck, and pharyngeal areas could be likely. In a population-based case control study, with adjustments for sex, education, birth year, alcohol use, and cigarette use, there was no significant association between oral SCC risk and marijuana use [42]. Similarly, in a large sample of patients with head and neck cancer, for those who ever smoked marijuana, there was no increased risk of cancer nor was there an association in those smoking one joint per day for 1 year. However, there was an increased risk of head and neck cancer in those who had smoked marijuana for more than 20 years and were never alcohol users compared with marijuana users who never used tobacco [48]. In another case-controlled study, no significant risk for head and neck cancer occurred for those people who had ever used marijuana; however, there was indication that higher exposure may lead to a greater risk [49]. Several other studies have not been conclusive to attribute risk of marijuana to esophageal and pharyngeal cancers when adjusted for confounders, especially cigarette smoking [50].

The risk of lung cancer has been examined in marijuana users. In a case-control study of lung cancer in marijuana

and performance in controlled driving-simulation studies,[36] which are a good predictor of real-world driving ability. Recent marijuana smoking and blood THC levels of 2 to 5 ng per milliliter are associated with substantial driving impairment.[37] According to a meta-analysis, the overall risk of involvement in an accident increases by a factor of about 2 when a person drives soon after using marijuana.[37] In an accident culpability analysis, persons testing positive for THC (typical minimum level of detection, 1 ng per milliliter), and particularly those with higher blood levels, were 3 to 7 times as likely to be responsible for a motor-vehicle accident as persons who had not used drugs or alcohol before driving.[38] In comparison, the overall risk of a vehicular accident increases by a factor of almost 5 for drivers with a blood alcohol level above 0.08%, the legal limit in most countries, and increases by a factor of 27 for persons younger than 21 years of age.[39] Not surprisingly, the risk associated with the use of alcohol in combination with marijuana appears to be greater than that associated with the use of either drug alone.[37]

Risk of Cancer and Other Effects on Health

The effects of long-term marijuana smoking on the risk of lung cancer are unclear. For example, the use of marijuana for the equivalent of 30 or more joint-years (with 1 joint-year of marijuana use equal to 1 cigarette [joint] of marijuana smoked per day for 1 year) was associated with an increased incidence of lung cancer and several cancers of the upper aerodigestive tract; however, the association disappeared after adjustment for potential confounders such as cigarette smoking.[40] Although the possibility of a positive association between marijuana smoking and cancer cannot be ruled out,[41] the evidence suggests that the risk is lower with marijuana than with tobacco.[40] However, the smoking of cigarettes that contain both marijuana and tobacco products is a potential confounding factor with a prevalence that varies dramatically among countries.

Marijuana smoking is also associated with inflammation of the large airways, increased airway resistance, and lung hyperinflation, associations that are consistent with the fact that regular marijuana smokers are more likely to report symptoms of chronic bronchitis than are nonsmokers[42]; however, the long-term effect of low levels of marijuana exposure does not appear to be significant.[43] The immunologic com petence of the respiratory system in marijuan smokers may also be compromised, as indicate by increased rates of respiratory infections an pneumonia.[44] Marijuana use has also been a sociated with vascular conditions that increa the risks of myocardial infarction, stroke, an transient ischemic attacks during marijuana i toxication.[45] The actual mechanisms underlyin the effects of marijuana on the cardiovascul and cerebrovascular systems are complex an not fully understood. However, the direct effec of cannabinoids on various target receptors (i.e CB1 receptors in arterial blood vessels) and th indirect effects on vasoactive compounds[46] ma help explain the detrimental effects of marijua na on vascular resistance and coronary microcu culation.[47]

Limitations of the Evidence and Gaps in Knowledge

Most of the long-term effects of marijuana us that are summarized here have been observe among heavy or long-term users, but multipl (often hidden) confounding factors detract fro our ability to establish causality (including th frequent use of marijuana in combination wit other drugs). These factors also complicate ou ability to assess the true effect of intrauterin exposure to marijuana. Indeed, despite the us of marijuana by pregnant women,[48] and anima models suggesting that cannabis exposure du ing pregnancy may alter the normal processe and trajectories of brain development,[49] our un derstanding of the long-term effects of prenata exposure to marijuana in humans is very poor.

The THC content, or potency, of marijuana as detected in confiscated samples, has bee steadily increasing from about 3% in the 1980 to 12% in 2012[50] (Fig. 1A). This increase in THC content raises concerns that the consequences o marijuana use may be worse now than in th past and may account for the significant in creases in emergency department visits by per sons reporting marijuana use[51] (Fig. 1B) and th increases in fatal motor-vehicle accidents.[35] Thi increase in THC potency over time also raise questions about the current relevance of th findings in older studies on the effects of mari juana use, especially studies that assessed long term outcomes.

The amount of THC in marijuana samples confiscated by police has been increasing steadily over the past few decades. In 2012, THC concentrations in marijuana averaged close to 15 percent, compared to around 4 percent in the 1980s. For a new user, this may mean exposure to higher concentrations of THC, with a greater chance of an adverse or unpredictable reaction. Increases in potency may account for the rise in emergency department visits involving marijuana use. For frequent users, it may mean a greater risk for addiction if they are exposing themselves to high doses on a regular basis. However, the full range of consequences associated with marijuana's higher potency is not well understood. For example, experienced users may adjust their intake in accordance with the potency or they may be exposing their brains to higher levels overall, or both.

Is Marijuana Addictive?

Contrary to common belief, marijuana is addictive. Estimates from research suggest that about 9 percent of users become addicted to marijuana; this number increases among those who start young (to about 17 percent, or 1 in 6) and among people who use marijuana daily (to 25-50 percent).

Long-term marijuana users trying to quit report withdrawal symptoms including irritability, sleeplessness, decreased appetite, anxiety, and drug craving, all of which can make it difficult to abstain. Behavioral interventions, including cognitive-behavioral therapy and motivational incentives (i.e., providing vouchers for goods or services to patients who remain abstinent) have proven to be effective in treating marijuana addiction. Although no medications are currently available, recent discoveries about the workings of the endocannabinoid system offer promise for the development of medications to ease withdrawal, block the intoxicating effects of marijuana, and prevent relapse.

How Does Marijuana Affect a User's Life?

Research shows marijuana may cause problems in daily life or make a person's existing problems worse. Heavy marijuana users generally report lower life satisfaction, poorer mental and physical health, more relationship problems, and less academic and career success compared to non-marijuana-using peers. For example, marijuana use is associated with a higher likelihood of dropping out of school. Several studies also associate workers' marijuana smoking with increased absences, tardiness, accidents, workers' compensation claims, and job turnover.