



Annual Review of Medicine

Adverse Impact of Cannabis on Human Health

Mark Chandy,^{1,2,3,4} Masataka Nishiga,^{1,2,3}
Tzu-Tang Wei,^{1,2,3,5} Naomi M. Hamburg,⁶
Kari Nadeau,⁷ and Joseph C. Wu^{1,2,3}

¹Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California, USA; email: mchandy2@uwo.ca, joewu@stanford.edu

²Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA

³Institute of Stem Cell Biology and Regenerative Medicine, Palo Alto, California, USA

⁴Department of Medicine, Western University, London, Ontario, Canada

⁵Department and Graduate Institute of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan

⁶Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine and Boston University School of Public Health, Boston, Massachusetts, USA

⁷Department of Environmental Health, Harvard T.H. Chan School of Public Health, Harvard University, Cambridge, Massachusetts, USA

Annu. Rev. Med. 2024. 75:7.1–7.15

The *Annual Review of Medicine* is online at
med.annualreviews.org

<https://doi.org/10.1146/annurev-med-052422-020627>

Copyright © 2024 by the author(s).
All rights reserved

Keywords

cannabis, cardiovascular disease, pulmonary disease, cannabis-induced psychosis, cannabis use disorder

Abstract

Cannabis, the most commonly used recreational drug, is illicit in many areas of the world. With increasing decriminalization and legalization, cannabis use is increasing in the United States and other countries. The adverse effects of cannabis are unclear because its status as a Schedule 1 drug in the United States restricts research. Despite a paucity of data, cannabis is commonly perceived as a benign or even beneficial drug. However, recent studies show that cannabis has adverse cardiovascular and pulmonary effects and is linked with malignancy. Moreover, case reports have shown an association between cannabis use and neuropsychiatric disorders. With growing availability, cannabis misuse by minors has led to increasing incidences of overdose and toxicity. Though difficult to detect, cannabis intoxication may be linked to impaired driving and motor vehicle accidents. Overall, cannabis use is on the rise, and adverse effects are becoming apparent in clinical data sets.



INTRODUCTION

Cannabis has been cultivated by humans for thousands of years for recreational and medicinal uses (1). Consumed in various modalities, including smoking, hookah, vaping, and edibles, cannabis is one of the most commonly used recreational drugs and is illicit in many areas of the world (2). With growing decriminalization and legalization, cannabis use has increased worldwide (3, 4).

There are over 500 chemicals in cannabis, and the chief psychoactive component, delta-9-tetrahydrocannabinol (Δ^9 -THC), is the most abundant cannabinoid (5). However, cannabis contains more than 100 other cannabinoids that are structurally similar to Δ^9 -THC, including cannabidiol (CBD), the second most abundant component, which is nonpsychotropic. The effects of cannabinoids are mediated by cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), which belong to the G protein-coupled receptor (GPCR) superfamily (6). CB1, the most abundant GPCR in the mammalian brain, regulates the psychoactive effects of Δ^9 -THC (**Figure 1**). CB1 is also expressed in other peripheral cells, tissues, and organs such as the heart, vasculature, and smooth muscle. CB2 is expressed in immune cells, particularly in macrophages. The cannabinoid receptors modulate adenylyl cyclase, ion channels, mitogen-activated protein (MAP) kinases [p44/42 MAP kinases, p38, extracellular signaling-regulated kinases (ERK), janus N-terminal kinase (JNK)], and ceramide signaling (7).

BENEFICIAL EFFECTS OF CANNABIS

A recent systematic review and meta-analysis found that cannabinoids such as Δ^9 -THC and CBD might be of benefit for chronic pain, spasticity, epilepsy, cancer, and neurological disorders (8). There are several reports describing the anti-inflammatory effects of cannabis and Δ^9 -THC (9). Δ^9 -THC has been reported to have apoptotic effects on immune cells (10, 11). Inflammatory cytokine production is also reduced after treatment with Δ^9 -THC (12, 13). In neurological disorders such as multiple sclerosis, Δ^9 -THC is also thought to exert beneficial effects due to immunosuppression (14). Indeed, several reports show that Δ^9 -THC can induce cytotoxicity in cancer, including acute lymphoblastic leukemia (15, 16).

CBD is reported to have anti-inflammatory properties (17) and might ameliorate inflammatory arthropathies (18). CBD is also described as having a neuroprotective effect (19) and is used for neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease (20, 21). Cannabinoids are known to induce sedation and analgesia and could be an alternative to opioids (22, 23). The adverse effects of opioids include constipation, overdose causing bradypnea, bradycardia, and death, as well as cardiovascular disease. Opioid misuse is exacerbated by the propensity for addiction and highlighted by the ongoing and unrelenting opioid crisis.

Medicinal marijuana has been used in HIV and cancer patients (24). Several forms of synthetic Δ^9 -THC have been approved by the US Food and Drug Administration (FDA) for treating chemotherapy-induced nausea and vomiting, as well as for HIV and anorexia: Marinol® (dronabinol), Syndros® (dronabinol), and Cesamet® (nabilone). More recently, synthetic cannabidiol, Epidiolex®, has been approved for treating epilepsy in children (25). However, while medicinal cannabis might be beneficial, its adverse effects are becoming evident with increased usage (24, 26).

The assumption that marijuana has pleiotropic benefits without any adverse consequences lacks supporting evidence in clinical practice. Some cannabinoids, such as CBD, might have beneficial effects; however, the overwhelming evidence from in vitro, in vivo, and clinical studies indicates that Δ^9 -THC is proinflammatory in the context of overall cardiovascular disease risk and likely a precipitant for myocardial infarction and increased mortality.

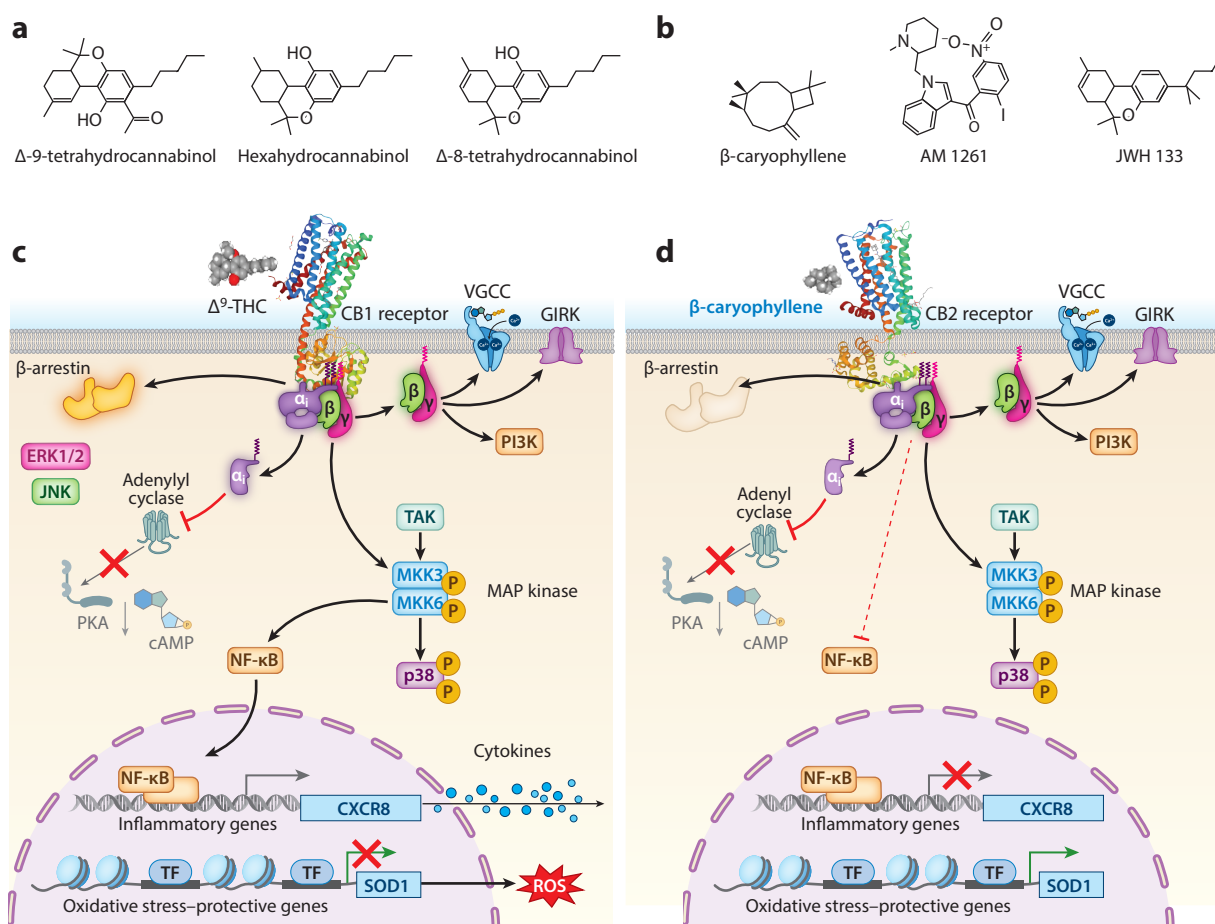


Figure 1

Cannabinoids and cognate receptors. (a) The molecular structures of three representative cannabinoid receptor 1 (CB1) agonists that cause psychoactive effects: Δ^9 -tetrahydrocannabinol (Δ^9 -THC), hexahydrocannabinol (HHC), and Δ^8 -tetrahydrocannabinol (Δ^8 -THC). (b) The molecular structures of three cannabinoid receptor 2 (CB2) agonists: β -caryophyllene (BCP), 2-iodo-5-nitrophenyl(1-((1-methylpiperidin-2-yl)methyl)-1H-indol-3-yl)methanone (AM 1261), and (6AR,10AR)-3-(1,1-Dimethylbutyl)-6A,7,10,10A-tetrahydro-6,6,9-trimethyl-6H-dibenzo[B,D]pyran (JWH 133). Chemical structures adapted from the National Center for Biotechnology Information. (c) CB1 activation causes inflammation and oxidative stress via multiple signaling pathways. Δ^9 -THC binding to the CB1 receptor activates the G protein-coupled receptor (GPCR). The G_i/o complex dissociates into the α_i , $\beta\gamma$, and β -arrestin subunits. The α_i subunit inhibits adenylyl cyclase, thereby decreasing cyclic AMP (cAMP) production and preventing protein kinase A (PKA) phosphorylation, which modulates transcription. The $\beta\gamma$ subunit activates the mitogen-activated pathway (MAP) and p38, which activate nuclear factor- κ B (NF- κ B), thus leading to the activation of inflammatory genes and downregulation of oxidative stress-protective genes. The $\beta\gamma$ subunit simultaneously affects voltage-gated calcium channels (VGCC), G protein-gated potassium channels (GIRK), and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway. (d) CB2 activation prevents NF- κ B translocation to the nucleus, thus blocking the expression of inflammatory genes and downregulating oxidative stress-protective genes. The $\beta\gamma$ subunit simultaneously affects VGCC, GIRK, and the PI3K/AKT pathway. Figure adapted from Reference 46 with permission, modified using BioRender.com.

ADVERSE CARDIOVASCULAR EFFECTS OF CANNABIS

The cardiovascular effects of cannabis are both acute and chronic. Acutely, the psychoactive component of cannabis, Δ^9 -THC, is associated with tachycardia, hypertension, platelet activation, and endothelial dysfunction (2). The chronic effects of cannabis are revealed in epidemiological studies that support the link between recreational cannabis use and heart disease, generally finding that cannabis increases the risk of cardiovascular disease, cardiomyopathy, and arrhythmias (2, 27, 28). Medical marijuana and synthetic cannabinoids are also associated with adverse cardiovascular effects (24, 26).

Inflammation plays a central role in the pathophysiology of atherosclerosis (29, 30). Chronic inflammation is speculated to accelerate atherosclerosis in diseases such as HIV, rheumatoid arthritis, and systemic lupus erythematosus (31–33). Δ^9 -THC has been described as promoting inflammation and oxidative stress via the CB1, MAP kinase activation, and NF- κ B pathways.

In addition to being the most abundantly expressed GPCR in the central nervous system, CB1 is also expressed in peripheral cells, tissues, and organs such as the heart and vasculature, and it has been implicated in atherosclerosis (34). CB1 activation occurs via the MAP kinase pathway, which causes oxidative stress, inflammation, and cell death in human coronary artery endothelial cells (35, 36). In contrast, CB2, while also expressed in the vasculature, is antiatherogenic (7). Preclinical studies have found that CB1 activation mediates increased oxidative stress and inflammation, which are implicated in diabetic retinopathy, cardiomyopathy, and endothelial dysfunction (36–38). Animal studies have shown a causal link between Δ^9 -THC via the atherogenic CB1 receptor (28, 39). The loss of the atheroprotective CB2 receptor exacerbates the progression of atherosclerosis (40, 41).

Historically, clinical associations between marijuana and cardiovascular disease were limited to case reports or case series (28), and these studies showed that even low doses of Δ^9 -THC are associated with adverse cardiovascular events (42, 43). A meta-analysis found an association between marijuana and cardiovascular disease. Frost et al. followed patients who were chronic marijuana users and found increased mortality (44). The landmark study by DeFilippis et al. showed a significant association between marijuana and cardiovascular disease in young patients with index myocardial infarction (27). Those using cannabis had a lower incidence of cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia when compared to nonusers. However, after adjusting for age, sex, diabetes, hypertension, peripheral vascular disease, smoking, high-density lipoprotein cholesterol, triglycerides, revascularization, creatinine, medications at discharge, and length of stay, DeFilippis et al. found that the adjusted hazard ratio for cardiovascular events was 2.09 [95% confidence interval (CI) 1.25–3.50; $p = 0.005$] for marijuana (27). They also noted the confounder of cigarette smoking with marijuana users significantly more likely to use tobacco (70.3% versus 49.1%; $p < 0.001$) than other participants. While cigarette smoking was strongly linked to marijuana use, the hazard ratio for marijuana and cardiovascular events was higher than for smoking tobacco cigarettes alone. Compared to a healthy nonsmoker, the adjusted hazard ratio in a current smoker was 1.7 (95% CI 1.3–2.2) for all-cause cardiovascular disease (45). The study was conducted in Massachusetts between 2000 and 2016, when recreational cannabis use was illicit there. Despite consequent concerns about participants not disclosing cannabis use, an increased incidence of cardiovascular events with a worse prognosis was observed among cannabis users.

In a recent study, Wei et al. described the adverse effect of Δ^9 -THC on the cardiovascular system using data from the UK Biobank, as well as from in vitro and in vivo models (46). Previous studies that showed a link between cannabis and cardiovascular disease were small and retrospective (27). The largest prospective cohort study to date, the UK Biobank, includes genetic and phenotypic data on 500,000 individuals ages 40 to 69 (47), thus providing a unique opportunity to

characterize relationships among clinical phenotypes. The UK Biobank analysis revealed an increased incidence of myocardial infarction for cannabis users under age 50 (0.53% versus 0.45%). Prior studies demonstrating an association between cannabis use and myocardial infarction were conducted on individuals who developed myocardial infarction before age 50 (27). Wei et al. (46) controlled for age, body mass index, and sex and developed a logistic regression model revealing that cannabis use was a statistically significant positive predictor for myocardial infarction. O-link analysis of blood from acute marijuana smokers found that 13 inflammatory cytokines associated with cardiovascular disease were elevated (46).

Using induced pluripotent stem cell (iPSC) disease modeling (48), Wei et al. (46) discovered that Δ^9 -THC caused toxicity, inflammation, and oxidative stress in iPSC-derived endothelial cells. Using siRNA and CRISPR interference knockdown of CB1 expression, they showed that the effects of Δ^9 -THC were dependent on CB1. The adverse effects of Δ^9 -THC were attenuated by CB1 antagonists such as rimonabant, which is associated with psychiatric side effects. However, virtual ligand modeling discovered that genistein is also a CB1 antagonist and could attenuate Δ^9 -THC-mediated inflammation and oxidative stress in iPSC-derived endothelial cells. Previous studies by Steffens et al. showed that low-dose Δ^9 -THC (1 mg/kg administered orally) was associated with reduced progression of atherosclerosis in *LDLR*^{-/-} mice (49). At low doses, the maximum concentration (c_{\max}) of Δ^9 -THC was 6 ng/mL and acted as an agonist of CB1 and CB2; CB2 antagonists abrogated these effects. However, in a 3.5% marijuana cigarette, the c_{\max} concentration of Δ^9 -THC was 169 ng/mL (50). Moreover, marijuana is now cultivated to produce higher concentrations of Δ^9 -THC, and e-cigarettes allow for vaping up to 85% Δ^9 -THC. Using the *LDLR*^{-/-} and *ApoE*^{-/-} mouse model, Wei et al. showed that intraperitoneal administration of Δ^9 -THC at 1 mg/kg achieved a c_{\max} dose of 130 ng/mL and caused endothelial dysfunction and atherosclerosis (46). More importantly, genistein ameliorated Δ^9 -THC-mediated inflammation, oxidative stress, and inflammation. This study was significant as it provided a mechanistic link between Δ^9 -THC and atherosclerotic cardiovascular disease.

Cardiomyopathy

Case reports and case series have described cannabis-induced cardiomyopathy (51). The link between cardiovascular disease and cannabis suggests that ischemic cardiomyopathy will increase with cannabis use. However, preclinical evidence that cannabinoids cause cardiotoxicity is conflicting. Rajesh et al. found that CB1 activation promoted the pathogenesis of diabetic cardiomyopathy in a mouse model of diabetic cardiomyopathy (37). However, Wei et al. found that Δ^9 -THC had no toxicity in primary cardiomyocytes, iPSC-derived cardiomyocytes, or a mouse model (46). Δ^9 -THC had minimal or no effect on contractility or beat rate in engineered heart cells composed of iPSC-derived cardiomyocytes and endothelial cells. RNA sequencing data sets found no significant effects on iPSC-derived cardiomyocytes or endothelial cells. Moreover, C57BL/6J mice exposed to 1 mg/kg Δ^9 -THC via intraperitoneal delivery for 1 month showed no evidence of cardiovascular dysfunction as assessed by echocardiography that interrogated systolic function and diastolic function using speckle tracking strain imaging.

Arrhythmias

Cannabis is associated with both supraventricular and ventricular arrhythmia. Multiple animal models and clinical data demonstrate immediate effects of tachycardia and hypertension, followed by bradycardia and hypotension with marijuana use (52). Despite lower blood pressure, cannabis users are at risk for dysrhythmias, including atrial fibrillation, atrial flutter, atrioventricular block, premature ventricular contractions, premature atrial contractions, ventricular tachycardia, and



ventricular fibrillation (53). With legalization and increased use of cannabis, cannabis use disorder is now associated with more arrhythmias, such as atrial fibrillation, requiring hospitalization and placing patients at a higher risk of stroke and embolic events (54, 55). Interestingly, the arrhythmias are more common in younger patients with cannabis use disorder, suggesting that the effects are due to the toxicity of cannabis. The precise mechanisms of the cannabis-induced arrhythmias are unclear and therefore merit further investigation given the severe consequences of dysrhythmias, such as atrial fibrillation causing stroke with potentially significant changes in quality of life for younger users.

ADVERSE PULMONARY EFFECTS OF CANNABIS

Widespread use of marijuana has highlighted the need to learn more about its potential deleterious side effects, particularly those affecting the respiratory system. Smoking is a major cause of cardiopulmonary disease, the leading cause of death worldwide (56). The harm from conventional cigarettes is from the combustion of tobacco products, exacerbated by long-term use due to nicotine addiction, which can lead to acute and long-term adverse changes in the lung, including chronic obstructive pulmonary disease (COPD), emphysema, idiopathic pulmonary fibrosis, and pulmonary hypertension (57). Smoking cannabis increases the respiratory burden of carbon monoxide and tar compared to traditional cigarettes (58). Moreover, cannabis and tobacco are often consumed together (59). Hancox et al. speculate that by mixing tobacco and cannabis, smokers can inhale more deeply and experience enhanced psychoactive effects and increased acute exposure to toxins (60). With deeper inhalation, cannabis users are at a higher risk of developing COPD and experiencing a more rapid decline in pulmonary function (61). The combined or synergistic effects of nicotine and Δ^9 -THC on the cardiopulmonary system are unclear and need further investigation. While the detrimental effects of conventional cigarette smoke are now well documented, the toxicities of e-cigarettes remain poorly understood (62).

E-cigarettes and other electronic nicotine dispenser systems are popular particularly among younger users (62). E-cigarettes do not produce carbon monoxide or toxins associated with conventional cigarettes. Because e-cigarettes do not involve combustion, they are speculated to aid in smoking cessation without some of the adverse effects of conventional cigarettes (62). However, the debate about whether e-cigarettes will provide long-term benefits or harm is ongoing, with limited data on the pulmonary effects (63). Although the components are toxic, the potentially adverse effects of e-cigarette liquids on the cardiopulmonary system are largely unknown. Given the increasing popularity of flavored e-cigarettes, their components and potential health risks must be studied systematically. E-cigarette and vaping-related acute lung injury (EVALI) have recently emerged as an urgent crisis (64). Illicit e-cigarettes are linked to the EVALI crisis. The content of illicit e-cigarettes are unknown because they do not undergo rigorous testing for contaminants as compared to commercially available sources. The US Centers for Disease Control and Prevention (CDC) estimates that over 2,500 patients have developed EVALI, with over 60 deaths from this mysterious illness (65). A breakthrough by the CDC eventually revealed the components associated with EVALI. While studying bronchoalveolar lavage specimens, investigators discovered nicotine, Δ^9 -THC, and vitamin E acetate as the most common components of e-cigarettes in EVALI patients (66). However, the mechanism by which these components and others affect the pulmonary tissue is unclear.

ADVERSE NEUROPSYCHIATRIC EFFECTS OF CANNABIS

Cannabinoids are used to treat various neurological disorders, including chronic pain, neurodegenerative diseases, and epilepsy. However, cannabinoids can also cause adverse neuropsychiatric

effects. The effects are both acute and chronic, and their incidence is increasing as a consequence of legalization.

Acute cannabis use causes sedation, analgesia, hypothermia, and hypomobility (67). Cannabis intoxication can impair motor coordination and judgment while producing euphoria and anxiety. Heavy cannabis use may alter neurological pathways and lead to addiction via the psychoactive component of cannabis, Δ^9 -THC (68). Withdrawal symptoms are also reported in a subset of patients (69).

Cannabis misuse has increased incidences of intoxication and cannabis hyperemesis syndrome (70). Chronic cannabis use causes dysregulation of the neuronal pathways in the central and enteric nervous systems, resulting in cyclical nausea, vomiting, and abdominal pain after cannabis use (71). The presentation resembles cyclical vomiting and can resolve with cannabis cessation.

Cannabis use disorder is the continued use of cannabis despite harm to the user or impaired social functioning (72). Cerda et al. found an increase in cannabis use disorder with legalization (73). Cannabis use disorder rose from 2.18% to 2.72% in respondents aged 12 to 17. In comparison, among respondents over 26 years of age, the proportion who reported an increase in frequent recreational cannabis use grew from 2.13% to 2.62%, and the proportion reporting cannabis use disorder increased from 0.9% to 1.23%.

Cannabinoids are associated with psychiatric conditions, including psychosis and mood disorders. Patients who use cannabis are more likely to have anxiety, depression, and bipolar disorder (74). Acutely, cannabis causes euphoria, but chronic use might perturb neurological pathways and cause mood disorders. However, cannabis use might be confounded with bipolar disorder and mitigate impulsive behavior (75), although cannabis use is associated with a higher rate of suicide in bipolar disorder.

Cannabis is also linked with psychosis. Using logistic regression analysis, Di Forti et al. found a link between high-potency cannabis use and the development of psychotic disorders (76). Exogenous cannabinoids affect the development of the central nervous system in rats, cause cognitive deficits, and alter cortical gene expression (77). A genetic variation of *AKT1* that affects dopamine signaling was found to increase the risk of psychosis in chronic cannabis users (78).

TRAUMA AND OVERDOSE

In the United States, motor vehicle accidents are a leading cause of mortality. Alcohol intoxication and, more recently, distracted driving while using cellular phones and other personal devices are associated with increased traffic accidents and fatalities (79). Cannabis intoxication is also associated with motor vehicle accidents (80). While acute alcohol intoxication can be detected with a breathalyzer or blood test, detecting cannabis intoxication is more difficult and requires novel methods (81, 82). Because cannabis can remain detectable in blood, saliva, and urine for hours to days, it is difficult to distinguish between acute intoxication and chronic use.

Misadventure is now being reported with cannabis edibles. Unlike smoking or vaping, edibles appear innocuous and are easy for anyone to ingest regardless of experience or age. A recent report suggests that pediatric emergency department visits have increased in Canada since the legalization of cannabis due to unintentional ingestion of cannabis (83). Pediatric patients present with analgesia and sedation, which can be fatal.

ADVERSE EFFECTS OF CANNABIS ON REPRODUCTION AND FERTILITY

Cannabis affects male fertility and conception. A systematic review found that chronic marijuana exposure reduced male fertility due to lower sperm count and abnormal sperm morphology,



mobility, and viability (84). Harlow et al. report that male preconception use of cannabis is associated with spontaneous abortion (85). Compared to nonusers, male users of cannabis at more than once per week increased the hazard ratio of spontaneous abortion by 2.0 (95% CI 1.2–3.1).

Prenatal exposure to cannabinoids can affect fetal development. Pregnant women frequently experience nausea and vomiting. Hyperemesis gravidarum is protracted nausea and vomiting that is only partly responsive to antiemetic medications. Cannabis is considered a benign herbal antiemetic and was recently found to significantly improve symptoms of hyperemesis gravidarum (86). However, the potential effects on the fetus are concerning. The CDC recommends against using marijuana during pregnancy because it is associated with abnormal neurological development and low birth weight (87). A systematic review found that prenatal exposure to cannabis is associated with maternal anemia, low birth weight, low neonatal length, and premature gestational age (88). Furthermore, Roncero et al. found a link between prenatal cannabis exposure and developmental and mental disorders in children, such as attention deficit hyperactivity disorder and depression (89).

CANNABIS AND MALIGNANCY

Cannabinoids are approved for treating cancer symptoms, including pain, nausea, and vomiting (90). Preclinical evidence suggests that cannabinoids might be effective therapy for glioblastoma multiforme, colon cancer, skin cancer, prostate cancer, and breast cancer (90). However, the clinical data on the efficacy of cannabinoids in cancer are unclear. There is a paucity of clinical trials showing cannabis improves cancer survival. After tumor debulking, only a single study on glioblastoma multiforme showed that Δ^9 -THC treatment caused a reduction in angiogenesis and tumor growth when assessed with magnetic resonance imaging on post-treatment biopsies (91).

Recent evidence suggests a link between marijuana use and cancer. A systematic review and meta-analysis found an association between marijuana use and cancer (92); while there was no association with head and neck cancer or oral cancer, testicular germ cell tumor was linked to marijuana use (odds ratio 1.36; 95% CI 1.03–1.81; $p = 0.03$; $I^2 = 0\%$). The study was underpowered to link marijuana use with lung cancer. However, a case-control study found that cannabis was associated with lung cancer (93). After adjusting for tobacco smoking, the risk of lung cancer increased with higher cannabis use. With legalization and increased use, the link between cancer and marijuana is expected to become more pronounced in the future and warrants further investigation.

CONCLUSION

Cannabis has been cultivated for thousands of years for recreation and medical therapy. In the early twentieth century, legal restrictions limited its consumption. Over the past 20 years, decriminalization and legalization have increased the availability of cannabis. Medicinal marijuana may benefit patients with chemotherapy-induced nausea and vomiting, HIV-induced cachexia, and neurodegenerative disorders. However, restrictions continue to limit research into the efficacy of medical marijuana. Preclinical studies and emerging epidemiological data suggest cannabis is expected to affect human health adversely in multiple ways.

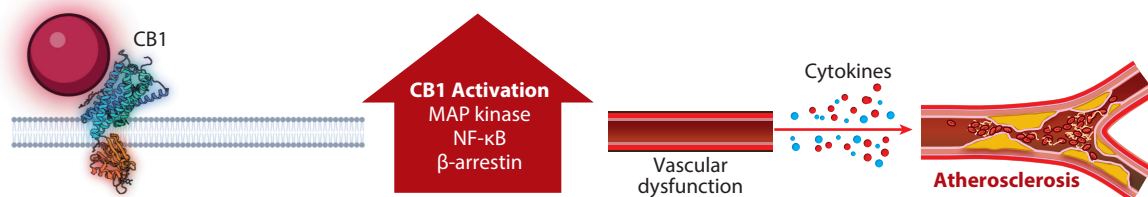
At the beginning of the twentieth century, tobacco cigarettes were incorporated into the American lifestyle and spread worldwide. We now know this led to dramatic increases in respiratory disease, cancer, and cardiovascular disease that caused millions of deaths. Cannabis might have medicinal benefits, but no medication is without side effects or adverse effects. Growing evidence suggests that expanding cannabis use will likely exacerbate cardiopulmonary disease and malignancy in the future. Historically, criminalizing cannabis has led to a disparity in enforcement



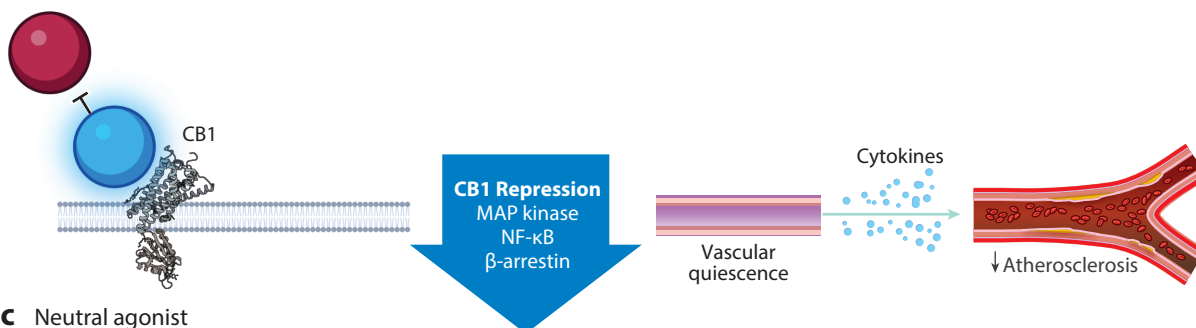
among racial groups. The incremental public health benefit of criminalizing cannabis might be outweighed by the social cost. More importantly, there is a lack of evidence to support such measures. Further research may also point to CB1 antagonists and CB2 agonists as a potential novel class of medical therapies (**Figure 2**).

The CB2 receptor is expressed mainly in immune and hematopoietic cells but also in peripheral cells, tissues, and organs including the central nervous system, enteric nervous system, heart, vasculature, liver, and pancreas (94). CB2 agonists modulate immune function and attenuate

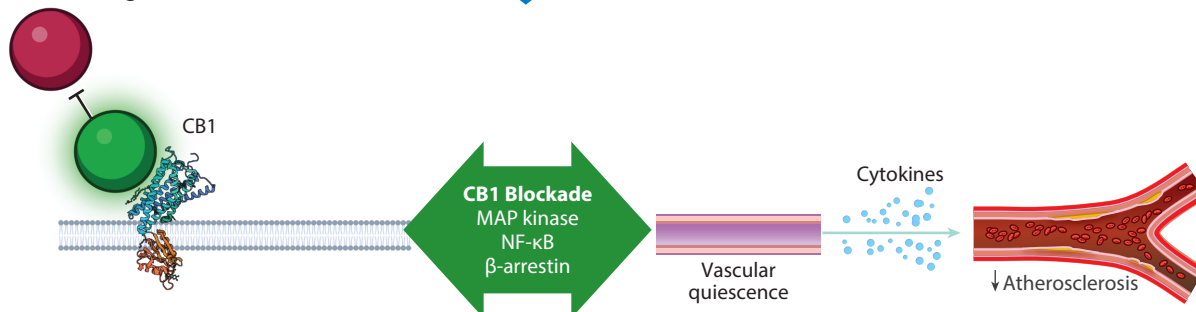
a CB1 agonist



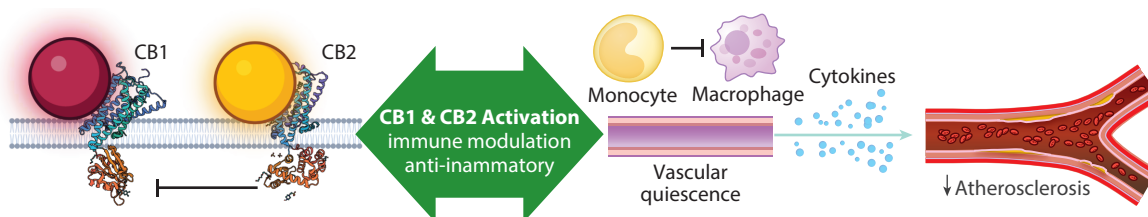
b Inverse agonist



c Neutral agonist



d CB2 agonist



(Caption appears on following page)

Figure 2 (Figure appears on preceding page)

Modulation of cannabinoid receptor activity. (a) Cannabinoid receptor 1 (CB1) agonists activate the CB1 receptor, causing inflammation, oxidative stress, and atherosclerosis. A CB1 agonist such as delta-9-tetrahydrocannabinol (Δ^9 -THC) (*red sphere*) binds to the CB1 receptor and activates the G protein-coupled receptor (GPCR), causing inhibition of adenylyl cyclase, phosphorylation of mitogen-activated pathway (MAP) kinase, translocation of nuclear factor- κ B (NF- κ B) to the nucleus, and activation of β -arrestin pathways. CB1 activation ultimately causes increased expression of inflammatory cytokines and oxidative stress, which promote atherosclerosis. (b) A CB1 receptor inverse agonist binds the agonists and prevents them from binding the CB1 receptor, modulates receptor function, and attenuates CB1-mediated atherosclerosis. An inverse agonist such as rimonabant (*blue sphere*) blocks CB1 agonist binding (*red sphere*) and downregulates CB1 receptor activity via the GPCR, thus preventing inhibition of adenylyl cyclase, MAP kinase phosphorylation, NF- κ B translocation to the nucleus, and β -arrestin pathway activation. Consequently, inverse agonists abrogate inflammation, oxidative stress, and atherosclerosis, which are mediated by CB1 agonist interactions. (c) A neutral antagonist blocks CB1 agonist binding and attenuates CB1 mediated atherosclerosis. A neutral antagonist such as genistein (*green sphere*) blocks the CB1 agonist (*red sphere*) without affecting the CB1 receptor or downstream pathways. Neutral antagonists also abrogate CB1-mediated inflammation, oxidative stress, and atherosclerosis. (d) CB2 agonists attenuate the adverse effects of CB1 activation by modulating the immune system, inflammation, and oxidative stress, thus preventing atherosclerosis. A CB2 agonist such as JWH 133 (*yellow sphere*) binds the CB2 receptor and counteracts the effects of a CB1 agonist (*red sphere*) binding the CB1 receptor by decreasing MAP kinase phosphorylation, preventing NF- κ B translocation, and modulating β -arrestin pathways. Because CB2 receptors are expressed on immune cells and the vasculature, CB2 agonists prevent the transformation of monocytes into macrophages in addition to suppressing vascular inflammation and oxidative stress, thereby promoting vascular quiescence and preventing atherosclerosis. Figure adapted from images created with BioRender.com.

vascular inflammation (95). Thus, CB2 agonists might be beneficial for treating inflammatory diseases such as inflammatory bowel disease, atherosclerosis, sepsis, traumatic brain injury, pain, and neurodegenerative diseases (96).

Novel CB1 antagonist therapies might mitigate the adverse effects of cannabis caused by Δ^9 -THC. CB1 signaling is involved in various pathophysiological processes, including smoking cessation, obesity, diabetes, coronary artery disease, atherosclerosis, liver cirrhosis, and cancer (34). CB1 antagonists are capable of attenuating Δ^9 -THC-mediated inflammation and oxidative stress. Experimental and clinical evidence supports the therapeutic potential of CB1 antagonists.

In 2006, rimonabant (Acomplia®) became the first CB1 antagonist approved in Europe for treating obesity (97). However, rimonabant was withdrawn in 2008 due to severe psychiatric side effects (98). Second- and third-generation compounds derived from rimonabant thus far have failed to translate to the clinic because of concerns about psychiatric effects and efficacy (99). To reduce the psychiatric side effects, pharmaceutical companies developed peripherally restricted CB1 antagonists with limited blood-brain barrier permeability and, in theory, less central nervous system exposure (100). Despite the restricted bioavailability, psychiatric side effects could not be completely excluded. Therefore, continuing efforts to discover novel CB1 antagonists with therapeutic potential that lack psychiatric side effects will be clinically important with the rapid growth of cannabis use worldwide.

DISCLOSURE STATEMENT

J.C.W. is a cofounder and a member of the Scientific Advisory Board of Greenstone Biosciences, and M.C. is a consultant for Greenstone Biosciences. This article was written independently of Greenstone Biosciences.

ACKNOWLEDGMENTS

We thank Blake Wu for his assistance with manuscript preparation. Owing to space limitations, we are unable to include all the important papers relevant to cannabinoid research, and we apologize to those investigators who have otherwise contributed substantially to this field. This work was supported by grants from the Stanford Cardiovascular Institute, Tobacco-Related

Disease Research Program (27IR-0012), Gootter-Jensen Foundation, American Heart Association (AHA) grant 17MERIT33610009 (J.C.W.), AHA grant 20YVNR3500014 (N.M.H.), and National Institutes of Health grant P01 HL152953 (K.N.).

LITERATURE CITED

1. Bridgeman MB, Abazia DT. 2017. Medicinal cannabis: history, pharmacology, and implications for the acute care setting. *PT Pharm. Ther.* 42:180–88
2. Page RL 2nd, Allen LA, Kloner RA, et al. 2020. Medical marijuana, recreational cannabis, and cardiovascular health: a scientific statement from the American Heart Association. *Circulation* 142:e131–52
3. Roterhmann M. 2020. What has changed since cannabis was legalized? *Health Rep.* 31:11–20
4. Martins SS, Segura LE, Levy NS, et al. 2021. Racial and ethnic differences in cannabis use following legalization in US states with medical cannabis laws. *JAMA Netw. Open* 4:e2127002
5. Atakan Z. 2012. Cannabis, a complex plant: different compounds and different effects on individuals. *Ther. Adv. Psychopharmacol.* 2:241–54
6. Hoffman AF, Lupica CR. 2013. Synaptic targets of Δ^9 -tetrahydrocannabinol in the central nervous system. *Cold Spring Harb. Perspect. Med.* 3:a012237
7. Ibsen MS, Connor M, Glass M. 2017. Cannabinoid CB1 and CB2 receptor signaling and bias. *Cannabis Cannabinoid Res.* 2:48–60
8. Bilbao A, Spanagel R. 2022. Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications. *BMC Med.* 20:259
9. Nagarkatti P, Pandey R, Rieder SA, et al. 2009. Cannabinoids as novel anti-inflammatory drugs. *Future Med. Chem.* 1:1333–49
10. Do Y, McKallip RJ, Nagarkatti M, Nagarkatti PS. 2004. Activation through cannabinoid receptors 1 and 2 on dendritic cells triggers NF- κ B-dependent apoptosis: novel role for endogenous and exogenous cannabinoids in immunoregulation. *J. Immunol.* 173:2373–82
11. Zhu W, Friedman H, Klein TW. 1998. Δ^9 -tetrahydrocannabinol induces apoptosis in macrophages and lymphocytes: involvement of Bcl-2 and caspase-1. *J. Pharmacol. Exp. Ther.* 286:1103–9
12. Srivastava MD, Srivastava BI, Brouhard B. 1998. Δ^9 tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells. *Immunopharmacology* 40:179–85
13. Smith SR, Terminelli C, Denhardt G. 2000. Effects of cannabinoid receptor agonist and antagonist ligands on production of inflammatory cytokines and anti-inflammatory interleukin-10 in endotoxemic mice. *J. Pharmacol. Exp. Ther.* 293:136–50
14. Pertwee RG. 2002. Cannabinoids and multiple sclerosis. *Pharmacol. Ther.* 95:165–74
15. Jia W, Hegde VL, Singh NP, et al. 2006. Δ^9 -tetrahydrocannabinol-induced apoptosis in Jurkat leukemia T cells is regulated by translocation of Bad to mitochondria. *Mol. Cancer Res.* 4:549–62
16. McKallip RJ, Lombard C, Fisher M, et al. 2002. Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. *Blood* 100:627–34
17. Soares RZ, Vuolo F, Dall'Igna DM, et al. 2015. Evaluation of the role of the cannabidiol system in an animal model of ischemia/reperfusion kidney injury. *Rev. Bras. Ter. Intensiva* 27:383–89
18. Lowin T, Tingting R, Zurmahr J, et al. 2020. Cannabidiol (CBD): a killer for inflammatory rheumatoid arthritis synovial fibroblasts. *Cell Death Dis.* 11:714
19. Sánchez AJ, García-Merino A. 2012. Neuroprotective agents: cannabinoids. *Clin. Immunol.* 142:57–67
20. Vallée A, Lecarpentier Y, Guillevin R, Vallée JN. 2017. Effects of cannabidiol interactions with Wnt/ β -catenin pathway and PPAR γ on oxidative stress and neuroinflammation in Alzheimer's disease. *Acta Biochim. Biophys. Sin.* 49:853–66
21. Santos NA, Martins NM, Sisti FM, et al. 2015. The neuroprotection of cannabidiol against MPP $^{+}$ -induced toxicity in PC12 cells involves trkA receptors, upregulation of axonal and synaptic proteins, neuritogenesis, and might be relevant to Parkinson's disease. *Toxicol. In Vitro* 30:231–40
22. Chandy M, Obal D, Wu JC. 2022. Elucidating effects of environmental exposure using human-induced pluripotent stem cell disease modeling. *EMBO Mol. Med.* 14:e13260
23. Obal D, Wu JC. 2020. Induced pluripotent stem cells as a platform to understand patient-specific responses to opioids and anaesthetics. *Br. J. Pharmacol.* 177:4581–94



24. Whiting PF, Wolff RF, Deshpande S, et al. 2015. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 313:2456–73
25. Hussain SA, Zhou R, Jacobson C, et al. 2015. Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy Behav.* 47:138–41
26. Volkow ND, Baler RD, Compton WM, Weiss SR. 2014. Adverse health effects of marijuana use. *N. Engl. J. Med.* 370:2219–27
27. DeFilippis EM, Singh A, Divakaran S, et al. 2018. Cocaine and marijuana use among young adults with myocardial infarction. *J. Am. Coll. Cardiol.* 71:2540–51
28. Pacher P, Steffens S, Hasko G, et al. 2018. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat. Rev. Cardiol.* 15:151–66
29. Libby P. 2002. Inflammation in atherosclerosis. *Nature* 420:868–74
30. Everett BM, MacFadyen JG, Thuren T, et al. 2020. Inhibition of interleukin-1 β and reduction in atherothrombotic cardiovascular events in the CANTOS Trial. *J. Am. Coll. Cardiol.* 76:1660–70
31. Shrestha S, Irvin MR, Grunfeld C, Arnett DK. 2014. HIV, inflammation, and calcium in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 34:244–50
32. Skeoch S, Bruce IN. 2015. Atherosclerosis in rheumatoid arthritis: Is it all about inflammation? *Nat. Rev. Rheumatol.* 11:390–400
33. Frostegard J. 2005. SLE, atherosclerosis and cardiovascular disease. *J. Intern. Med.* 257:485–95
34. Sugamura K, Sugiyama S, Nozaki T, et al. 2009. Activated endocannabinoid system in coronary artery disease and antiinflammatory effects of cannabinoid 1 receptor blockade on macrophages. *Circulation* 119:28–36
35. Liu J, Gao B, Mirshahi F, et al. 2000. Functional CB1 cannabinoid receptors in human vascular endothelial cells. *Biochem. J.* 346(Pt. 3):835–40
36. Rajesh M, Mukhopadhyay P, Hasko G, et al. 2010. Cannabinoid-1 receptor activation induces reactive oxygen species-dependent and -independent mitogen-activated protein kinase activation and cell death in human coronary artery endothelial cells. *Br. J. Pharmacol.* 160:688–700
37. Rajesh M, Batkai S, Kechrid M, et al. 2012. Cannabinoid 1 receptor promotes cardiac dysfunction, oxidative stress, inflammation, and fibrosis in diabetic cardiomyopathy. *Diabetes* 61:716–27
38. El-Remessy AB, Rajesh M, Mukhopadhyay P, et al. 2011. Cannabinoid 1 receptor activation contributes to vascular inflammation and cell death in a mouse model of diabetic retinopathy and a human retinal cell line. *Diabetologia* 54:1567–78
39. Dol-Gleizes F, Paumelle R, Visentin V, et al. 2009. Rimonabant, a selective cannabinoid CB1 receptor antagonist, inhibits atherosclerosis in LDL receptor-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* 29:12–18
40. Netherland CD, Pickle TG, Bales A, Thewke DP. 2010. Cannabinoid receptor type 2 (CB2) deficiency alters atherosclerotic lesion formation in hyperlipidemic Ldlr-null mice. *Atherosclerosis* 213:102–8
41. Hoyer FF, Steinmetz M, Zimmer S, et al. 2011. Atheroprotection via cannabinoid receptor-2 is mediated by circulating and vascular cells in vivo. *J. Mol. Cell Cardiol.* 51:1007–14
42. Draz EI, Oreby MM, Elsheikh EA, et al. 2017. Marijuana use in acute coronary syndromes. *Am. J. Drug Alcohol Abuse* 43:576–82
43. Patel RS, Katta SR, Patel R, et al. 2018. Cannabis use disorder in young adults with acute myocardial infarction: trend inpatient study from 2010 to 2014 in the United States. *Cureus* 10:e3241
44. Frost L, Mostofsky E, Rosenbloom JI, et al. 2013. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am. Heart J.* 165:170–75
45. McEvoy JW, Blaha MJ, DeFilippis AP, et al. 2015. Cigarette smoking and cardiovascular events: role of inflammation and subclinical atherosclerosis from the MultiEthnic Study of Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 35:700–9
46. Wei TT, Chandy M, Nishiga M, et al. 2022. Cannabinoid receptor 1 antagonist genistein attenuates marijuana-induced vascular inflammation. *Cell* 185:1676–93.e23
47. Bycroft C, Freeman C, Petkova D, et al. 2018. The UK Biobank resource with deep phenotyping and genomic data. *Nature* 562:203–9



48. Paik DT, Chandy M, Wu JC. 2020. Patient and disease-specific induced pluripotent stem cells for discovery of personalized cardiovascular drugs and therapeutics. *Pharmacol. Rev.* 72:320–42
49. Steffens S, Veillard NR, Arnaud C, et al. 2005. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature* 434:782–86
50. Huestis MA. 2007. Human cannabinoid pharmacokinetics. *Chem. Biodivers.* 4:1770–804
51. Kariyanna PT, Jayarangaiah A, Singh N, et al. 2018. Marijuana induced myocarditis: a new entity of toxic myocarditis. *Am. J. Med. Case Rep.* 6:169–72
52. Sultan SR, Millar SA, O'Sullivan SE, England TJ. 2018. A systematic review and meta-analysis of the in vivo haemodynamic effects of Δ^9 -tetrahydrocannabinol. *Pharmaceuticals* 11:13
53. Richards JR, Blohm E, Toles KA, et al. 2020. The association of cannabis use and cardiac dysrhythmias: a systematic review. *Clin. Toxicol.* 58:861–69
54. Patel RS, Gonzalez MD, Ajibawo T, Baweja R. 2021. Cannabis use disorder and increased risk of arrhythmia-related hospitalization in young adults. *Am. J. Addict.* 30:578–84
55. Chouairi F, Miller PE, Guha A, et al. 2021. Cannabis use disorder among atrial fibrillation admissions, 2008–2018. *Pacing Clin. Electrophysiol.* 44:1934–38
56. Ezzati M, Lopez AD. 2003. Estimates of global mortality attributable to smoking in 2000. *Lancet* 362:847–52
57. Natl. Cent. Chronic Dis. Prev. Health Promot. (US) Off. Smok. Health. 2014. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta, GA: CDC
58. Wu TC, Tashkin DP, Djahed B, Rose JE. 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. *N. Engl. J. Med.* 318:347–51
59. Jayakumar N, Chaiton M, Goodwin R, et al. 2021. Co-use and mixing tobacco with cannabis among Ontario adults. *Nicotine Tob. Res.* 23:171–78
60. Hancox RJ, Poulton R, Ely M, et al. 2010. Effects of cannabis on lung function: a population-based cohort study. *Eur. Respir. J.* 35:42–47
61. Tan WC, Bourbeau J, Aaron SD, et al. 2019. The effects of marijuana smoking on lung function in older people. *Eur. Respir. J.* 54:1900826
62. Benowitz NL, Fraiman JB. 2017. Cardiovascular effects of electronic cigarettes. *Nat. Rev. Cardiol.* 14:447–56
63. Gotts JE, Jordt S-E, McConnell R, Tarran R. 2019. What are the respiratory effects of e-cigarettes? *BMJ* 366:l5275
64. Butt YM, Smith ML, Tazelaar HD, et al. 2019. Pathology of vaping-associated lung injury. *N. Engl. J. Med.* 381:1780–81
65. Hayes D Jr., Board A, Calfee CS, et al. 2022. Pulmonary and critical care considerations for e-cigarette, or vaping, product use-associated lung injury. *Chest* 162:256–64
66. Blount BC, Karwowski MP, Shields PG, et al. 2019. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *N. Engl. J. Med.* 382:697–705
67. Martin BR, Dewey WL, Harris LS, Beckner J. 1975. Marihuana-like activity of new synthetic tetrahydrocannabinols. *Pharmacol. Biochem. Behav.* 3:849–53
68. Adams IB, Martin BR. 1996. Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91:1585–614
69. Bonnet U, Preuss UW. 2017. The cannabis withdrawal syndrome: current insights. *Subst. Abuse Rehabil.* 8:9–37
70. Gajendran M, Sifuentes J, Bashashati M, McCallum R. 2020. Cannabinoid hyperemesis syndrome: definition, pathophysiology, clinical spectrum, insights into acute and long-term management. *J. Investig. Med.* 68:1309–16
71. Chu F, Cascella M. 2023. Cannabinoid hyperemesis syndrome. In *StatPearls*. Treasure Island, FL: StatPearls. Updated July 4, 2022. <https://www.ncbi.nlm.nih.gov/books/NBK549915/>
72. Patel J, Marwaha R. 2023. Cannabis use disorder. In *StatPearls*. Treasure Island, FL: StatPearls. Updated July 11, 2022. <https://www.ncbi.nlm.nih.gov/books/NBK538131/>
73. Cerda M, Mauro C, Hamilton A, et al. 2020. Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiatry* 77:165–71



74. Lucatch AM, Coles AS, Hill KP, George TP. 2018. Cannabis and mood disorders. *Curr. Addict. Rep.* 5:336–45
75. Pinto JV, Medeiros LS, Santana da Rosa G, et al. 2019. The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: a systematic review with meta-analysis and meta-regression. *Neurosci. Biobehav. Rev.* 101:78–84
76. Di Forti M, Quattrone D, Freeman TP, et al. 2019. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry* 6:427–36
77. Campolongo P, Trezza V, Cassano T, et al. 2007. Perinatal exposure to delta-9-tetrahydrocannabinol causes enduring cognitive deficits associated with alteration of cortical gene expression and neurotransmission in rats. *Addict. Biol.* 12:485–95
78. Di Forti M, Iyegbe C, Sallis H, et al. 2012. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. *Biol. Psychiatry* 72:811–16
79. Kochling J, Geis B, Chao CM, et al. 2021. The hazardous (mis)perception of Self-estimated Alcohol intoxication and Fitness to drive—an avoidable health risk: the SAFE randomised trial. *Harm. Reduct. J.* 18:122
80. Rogeberg O, Elvik R. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 111:1348–59
81. Doucette ML, Frattaroli S, Vernick JS. 2018. Oral fluid testing for marijuana intoxication: enhancing objectivity for roadside DUI testing. *Inj. Prev.* 24:78–80
82. Lynch KL, Luo YR, Hooshfar S, Yun C. 2019. Correlation of breath and blood Δ^9 -tetrahydrocannabinol concentrations and release kinetics following controlled administration of smoked cannabis. *Clin. Chem.* 65:1171–79
83. Yeung MEM, Weaver CG, Hartmann R, et al. 2021. Emergency department pediatric visits in Alberta for cannabis after legalization. *Pediatrics* 148:e2020045922
84. Payne KS, Mazur DJ, Hotaling JM, Pastuszak AW. 2019. Cannabis and male fertility: a systematic review. *J. Urol.* 202:674–81
85. Harlow AF, Wesselink AK, Hatch EE, et al. 2021. Male preconception marijuana use and spontaneous abortion: a prospective cohort study. *Epidemiology* 32:239–47
86. Koren G, Cohen R. 2020. The use of cannabis for hyperemesis gravidarum (HG). *J. Cannabis Res.* 2:4
87. Natl. Acad. Sci. Eng. Med. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: Natl. Acad. Press
88. Gunn JK, Rosales CB, Center KE, et al. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. *BMJ Open* 6:e009986
89. Roncero C, Valriberas-Herrero I, Mezzatesta-Gava M, et al. 2020. Cannabis use during pregnancy and its relationship with fetal developmental outcomes and psychiatric disorders: a systematic review. *Reprod. Health* 17:25
90. Bowles DW, O'Bryant CL, Camidge DR, Jimeno A. 2012. The intersection between cannabis and cancer in the United States. *Crit. Rev. Oncol. Hematol.* 83:1–10
91. Guzman M, Duarte MJ, Blazquez C, et al. 2006. A pilot clinical study of Δ^9 -tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br. J. Cancer* 95:197–203
92. Ghasemiesfe M, Barrow B, Leonard S, et al. 2019. Association between marijuana use and risk of cancer: a systematic review and meta-analysis. *JAMA Netw. Open* 2:e1916318
93. Aldington S, Harwood M, Cox B, et al. 2008. Cannabis use and risk of lung cancer: a case-control study. *Eur. Respir. J.* 31:280–86
94. Pacher P, Mechoulam R. 2011. Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Prog. Lipid Res.* 50:193–211
95. Turcotte C, Blanchet MR, Laviolette M, Flamand N. 2016. The CB₂ receptor and its role as a regulator of inflammation. *Cell Mol. Life Sci.* 73:4449–70
96. Bie B, Wu J, Foss JF, Naguib M. 2018. An overview of the cannabinoid type 2 receptor system and its therapeutic potential. *Curr. Opin. Anaesthesiol.* 31:407–14
97. Despres JP, Golay A, Sjostrom L. 2005. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N. Engl. J. Med.* 353:2121–34



98. Onakpoya IJ, Heneghan CJ, Aronson JK. 2016. Worldwide withdrawal of medicinal products because of adverse drug reactions: a systematic review and analysis. *Crit. Rev. Toxicol.* 46:477–89
99. Cinar R, Iyer MR, Kunos G. 2020. The therapeutic potential of second and third generation CB₁R antagonists. *Pharmacol. Ther.* 208:107477
100. Fulp A, Bortoff K, Seltzman H, et al. 2012. Design and synthesis of cannabinoid receptor 1 antagonists for peripheral selectivity. *J. Med. Chem.* 55:2820–34

