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Marijuana: Respiratory Tract Effects

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Abstract Marijuana is the most commonly used drug of abuse in the USA. It is commonly abused through inhalation and therefore has effects on the lung that are similar to tobacco smoke, including increased cough, sputum production, hyperinflation, and upper lobe emphysematous changes. However, at this time, it does not appear that marijuana smoke contributes to the development of chronic obstructive pulmonary disease. Marijuana can have multiple physiologic effects such as tachycardia, peripheral vasodilatation, behavioral and emotional changes, and possible prolonged cognitive impairment. The carcinogenic effects of marijuana are unclear at this time. Studies are mixed on the ability of marijuana smoke to increase the risk for head and neck squamous cell carcinoma, lung cancer, prostate cancer, and cervical cancer. Some studies show that marijuana is protective for development of malignancy. Marijuana smoke has been shown to have an inhibitory effect on the immune system. Components of cannabis are under investigation as treatment for autoimmune diseases and malignancy. As marijuana becomes legalized in many states for medical and recreational use, other forms of tetrahydrocannabinol (THC) have been developed, such as food products and beverages. As most research on marijuana at this time has been on whole marijuana smoke, rather than THC, it is difficult to determine if the currently available data is applicable to these newer products.

Keywords Marijuana · Chronic obstructive pulmonary disease · Malignancy · Chronic bronchitis · Immune system

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Introduction

In the USA, marijuana was used medicinally until the passage of the Marijuana Tax Act in 1937, which made use illegal. Under the controlled substance act of 1970, marijuana was classified as a Schedule I drug. Schedule I drugs are defined as drugs with no currently accepted medical use and a high potential for abuse [1]. Since then, 18 states have legalized marijuana for different degrees of medical use, and two states have legalized marijuana for personal consumption. To date, federal law has not changed its stance on marijuana, but federal prosecution of users has been limited.

Data from the 2011 National Survey on Drug Use and Health show that marijuana is the most commonly used drug of abuse [2]. Annual use of marijuana has increased over the past decade to 7.0 % of the population or 18.1 million people age 12 or older. In 2011, 2.6 million people used marijuana for the first time, which averages to 7,200 new users per day. On average, about five million people are using marijuana on a daily or nearly daily basis. Despite the recent increase in use, the number of current or new users is still lower than it was at the peak of use in the 1970s (Fig. 1).

Marijuana is derived from the *Cannabis sativa* plant. The stalks, leaves, flowers, and seeds of the plant contain cannabinoids, which are the active ingredients. The drug is usually prepared by drying the flowering top and leaves of the plant. Over 400 compounds have been found in marijuana including 60 different cannabinoids [3]. The cannabinoid 1-delta-9-tetrahydrocannabinol (THC) was identified

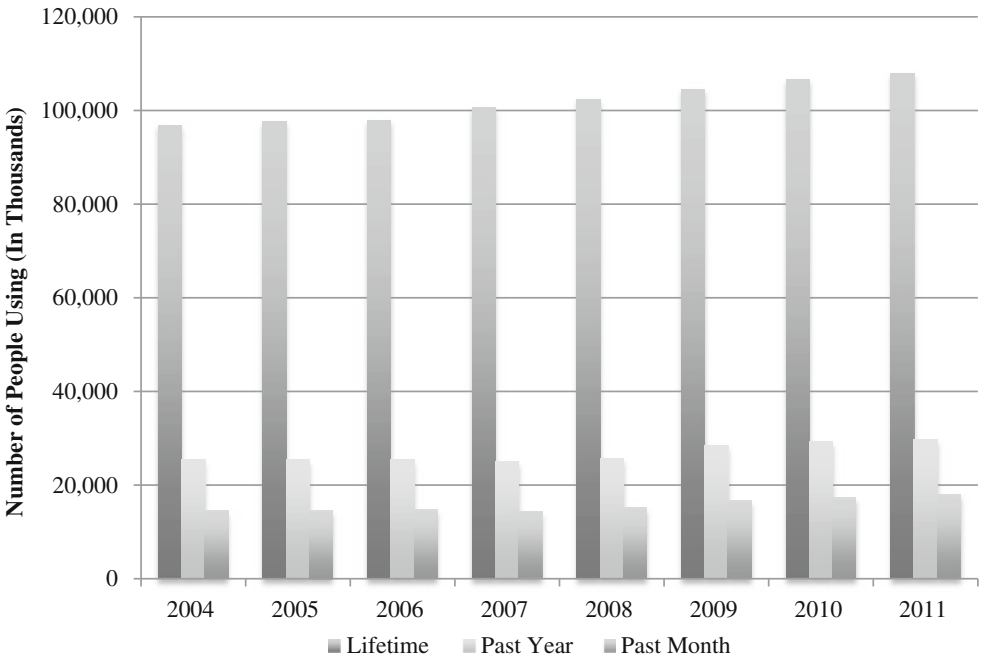

Fig. 1 Number of people (in thousands) using marijuana in their lifetime, past year, and past month for the years 2004–2011. Graph created with data from the National Survey on Drug Use and Health. Marijuana use declined from 1979 to 1990, before leveling off. However, current use is increasing over recent years (see [1])

in 1964 [4], and is thought to be responsible for most of the psychoactive effects of the drug. Other cannabinoids have been identified such as cannabinol (CBN), cannabidiol (CBD), and delta-8-THC. CBD does not have psychoactive effects, though has been shown to have anti-epileptic, anxiolytic, and antiemetic actions as well as causing drug-induced prolongation of sleep [5]. The average content of dried marijuana leaves confiscated from the USA between 1993 and 2008 was 4.5 % THC, 0.4 % CBD, and 0.3 % CBN [6]. The cannabinoid content in hashish (a more concentrated form) was 14.1 % THC, 2.4 % CBD, and 1.9 % CBN [6] (Fig. 2).

The composition of marijuana smoke and tobacco smoke are complex, but thought to be similar, with the exception of the active ingredients (cannabinoids and nicotine, respectively). Therefore, the respiratory effects of marijuana smoke are, in general, similar to tobacco, including chronic bronchitis, chronic obstructive pulmonary disease (COPD), and emphysema, as well as development of pulmonary, laryngeal, and head and neck cancer [3, 7]. However, studies proving these associations are mixed and have significant limitations.

Research on the potential health effects of marijuana is ongoing. Despite the research, their remains debate about potential health consequences. This is due to a multitude of factors. First, though research can be performed using purified THC, marijuana smoke contains multiple different compounds. Second, studies of marijuana users often are confounded by concurrent use of tobacco or other drugs. Finally, given that marijuana is an illicit substance, use may be underreported. The health effects of marijuana are summarized in Table 1.

Pharmacology

In the past, the main exposure to cannabinoids was through smoking of marijuana joints. As medicinal use of marijuana has increased, multiple different products containing THC have been developed, including oils, baked products, and beverages. Ways of smoking marijuana have also changed with the advent of vaporizers, which allow the combustion and release of THC with reduced combustion-related by-products of traditional marijuana smoke. The average THC content of a joint in the 1960–1970s contained about 10 mg of THC. Current marijuana rolled cigarettes or joints may contain 150 mg of THC, or up to 300 mg if hashish oil is added [3]. The THC content in edibles and oils is not standardized and has not been well studied.

Marijuana Smoke Composition

Over 6,000 different chemical components have been found in tobacco smoke, with several thousand-fold more trace components [8]. Though marijuana smoke has not been as well characterized, studies have found that the pyrolization of both marijuana and tobacco results in smoke with similar components [9–24]. Both tobacco and marijuana smoke contain vinyl chlorides, phenol, nitrosamines, reactive oxygen species, and various polycyclic aromatic hydrocarbons (PAH), which are known carcinogens and co-carcinogens [25]. Furthermore, marijuana tar has been found to have higher concentrations of benzo(a)pyrene, a procarcinogenic PAH, than tobacco tar [25].

When evaluating the concentrations of individual chemicals in marijuana smoke and tobacco smoke, the data is conflicting.

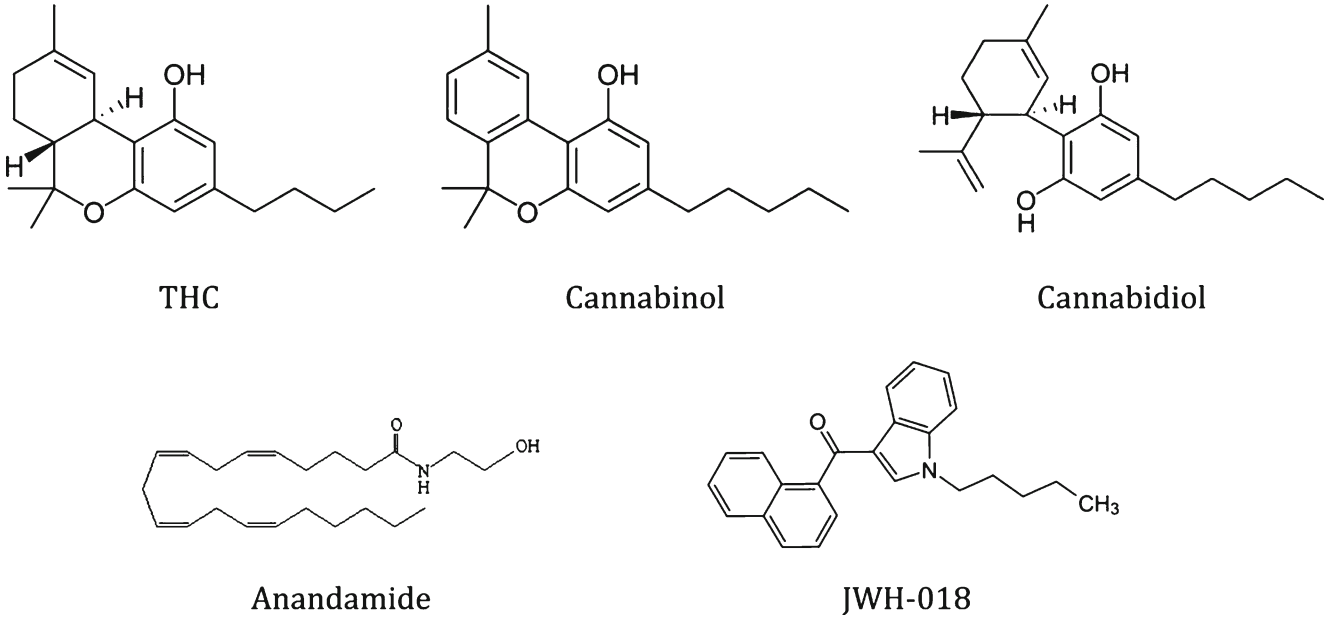

Fig. 2 Molecular structure of natural cannabinoids delta-9-tetrahydracannabinol (THC), cannabinol, cannabidiol, endogenous cannabinoid anandamide, and synthetic cannabinoid JWH-018

Huber et al. [8] compiled data from multiple studies and determined that, in general, marijuana smoke tended to contain higher amounts of ammonia, hydrogen cyanide, and some PAH. In this compilation, tobacco smoke was found to contain higher amounts of carbon monoxide. A recent study by Moir et al. [26] found that marijuana smoke contained three to five times higher levels of nitrogen, both as nitrate and ammoniacal nitrogen, hydrogen cyanide, and aromatic amines. Ammonia was found in marijuana smoke at levels 20 times higher than tobacco smoke. PAH, formaldehyde, carbon monoxide, and acetaldehyde were found at higher levels in tobacco smoke than marijuana smoke. A summary of the components of marijuana and tobacco smoke are found in Table 2.

The way a marijuana cigarette is smoked can also change what is delivered to the lungs. Smokers of marijuana have been found to inhale deeply and hold the smoke in their lungs [27, 28]. The holding of smoke in the lungs has been shown to result in higher delivery of tar, carbon monoxide, and THC to the lungs [29]. Relative to tobacco smokers, smokers of marijuana may inhale more than three times as much tar, and more than one third more tar may be deposited in the respiratory tract [28]. These findings, along with histopathologic changes, have led to the hypothesis that marijuana smoke is carcinogenic [30].

Given the potential carcinogenicity of marijuana smoke from combustion, alternate mechanisms of delivery have been developed. Vaporizers are machines that heat cannabis to a temperature where active cannabis vapors form but below the temperature at which smoke and other carcinogens form [31]. This delivery system has been found to have similar delivery of THC as smoking, with reduced levels of carbon monoxide [32]. Analysis of vapor smoke demonstrated higher levels of THC than smoking, with lower levels of by-products than joint smoke. However, in this

Table 1 Potential health consequences of marijuana smoking

Organ system	Manifestation
Cell metabolism	Decreased cell proliferation, protein synthesis
Genetic	Abnormal mitoses, DNA synthesis alterations
Immunologic	Impairs the following: cell-mediated immunity, macrophage activation, accessory T cell, cytotoxic T cell, and NK cell function. Modifies cytokine release
Neurologic	Acute: behavioral and emotional changes, impaired psychomotor performance, psychotic reaction
	Chronic: possible prolonged cognitive impairment
Cardiovascular	Peripheral vasodilatation, tachycardia, increased oxygen consumption
Reproductive	Postural hypotension, syncope
	Gynecomastia, decreased sperm count, impaired ovulation

Table 2 Components of marijuana and tobacco smoke

Component	Huber et al.		Moir et al.			
			ISO		Extreme	
	Marijuana	Tobacco	Marijuana	Tobacco	Marijuana	Tobacco
Acetaldehyde	1,200	980	448±44*	872±101	1,021±99*	1,555±222
Acetone	443	578	237±23*	454±44	514±32*	826±93
Acrolein	92	85	54.3±4.5*	125±13	148±13*	251±32
Ammonia	228	198	720±84*	35.5±2.4	1,315±106	67±9.9
Benz(a)anthracene	75	43	26.2±3.4*	30.5±2.5	43.1±7.9*	52±5.8
Benz(a)pyrene	31	22	8.67±1.12*	14.3±1.2	15.5±2.9*	25.1±2.5
Benzene	76	67	58.3±5.9	62.2±3.5	84.4±8.9*	94.6±2.6
Carbon Monoxide (ppm/cig)	2,600	4,100				
Carbon monoxide (mg/cig)			13.4±1.6*	20.8±1.9	35.3±2.9*	41.5±4.0
Hydrogen cyanide	532	498	525±46*	208±24	1,668±159*	320±29
Isoprene	83	310	74±6.5*	286±15	132±19*	540±18
m- and *p*-Cresol	54.4	65	57.8±6.7	55.4±3.8	157±12*	114±7
Naphthalene	3,000	1,200	2,070±290*	2,907±159	4,459±646	4,908±456
o-Cresol	17.9	24	17.6±1.5	25.5±1.9	46.8±3.9*	51.5±3.3
Phenol	76.8	39	91.5±10.5*	137±11	265±20	283±20

Tobacco and marijuana smoke have many similar components. The ISO smoking group represents a puff volume of 35 mL, a puff duration of 2 s, and a puff interval of 60 s. The extreme conditions are thought to more accurately represent the way that marijuana is smoked and used a puff volume of 70 mL, a puff duration of 2 s, and a puff interval of 30 s. All concentrations are in micrograms unless otherwise noted. Table comprised from data from [8] and [26]

*Denotes statistically significant difference between marijuana and tobacco smoke for Moir et al. [26]

study, the by-products were not analyzed for content [33]. A small non-randomized trial of 12 frequent marijuana smokers who switched to vaporizers showed a significant reduction in respiratory symptoms and improvement in forced vital capacity (FVC) [34].

Absorption and Metabolism

The rate of absorption of cannabis is dependent on both the potency of the specific cannabis product and the mechanism of consumption (IV, inhalational, or oral). About 10–30 % of available THC is absorbed after smoking, as 50 % of THC is lost from smoke escaping into the air or respiratory dead space, and more is lost with combustion [7]. After smoking, THC is rapidly transferred from the lungs to the blood, with peak concentrations occurring between 3 and 10 min [35, 36]. When injected in the IV form, similar times to peak were observed, with higher concentrations than with inhalation [35]. Onset of psychotropic effects is noted within seconds to minutes with a duration of 2–3 h [7]. This is in contrast with oral ingestion, where onset is variable, usually 0.5–2 h, and effects can last 5–6 h [7]. In both cases, THC levels do not correlate with degree of psychotropic effects [35].

Once absorbed, THC follows a biphasic distribution pattern and eventually accumulates in lipophilic tissue. Initially, THC distributes to highly vascularized organs such as the liver, kidneys, heart, and muscle tissue. The distribution half-life is less than 10 min following smoking or IV injection [36, 37]. Following initial distribution, THC accumulates more slowly in body fat and less vascularized tissue.

THC is metabolized by hepatic microsomal hydroxylation and oxidation by CYP 2C9 and 3A4 in the liver [38]. The cytochrome 2C9 is responsible for the oxidation of THC at the C11 position, to its major active metabolite 11-hydroxy-Δ^9-THC (11-OH-THC) [39, 40]. CYP 3A4 is responsible for oxidation at the 8β-position [39]. Subsequent oxidation of 11-OH-THC leads to the major inactive metabolite 11-nor-delta9-carboxy-tetrahydrocannabino-9-carboxylic acid (THC-COOH), which is then eliminated in the urine. The UDP-glucuronosyltransferase enzymes also play a role in the metabolism of THC and its metabolites [41]. Fifteen to twenty percent of a dose of THC is eliminated as urinary metabolites, and 65 % is eliminated by fecal excretion as 11-OH-THC and THC-COOH [42]. Data from in vitro studies suggests that THC can inhibit 2C9, though to a lesser degree than CBD [43]. It is unclear if this effect is clinically relevant.

CBD is metabolized through the CYP 2C19 pathway in the liver. It has been found to be a potent inhibitor of CYP1A1, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 [44]. The degree of in vivo inhibition is unclear at

this time. As these enzymes are important in the metabolism of many common drugs, the potential for drug/drug interactions is a concern, and further research is needed.

Cannabinoid Receptor Physiology

Cannabinoid receptors have been isolated in central nervous system tissue of multiple species including rat [45], mouse [46, 47], bovine, feline [48], leech [49], puffer fish [50], and newt [51]. The discovery of endogenous cannabinoids (endocannabinoids) has accelerated research on the cannabinoid receptor system. The first endocannabinoid was identified in 1992 and was named "anandamide" after the Sanskrit word for "bliss" [52]. Next, 2-arachidonylglyerol was discovered in 1995 [53, 54]. Finally, in 2001, 2-arachiodonyl glycerol ether (noladin ether) was identified in porcine brain [55].

There are two main cannabinoid receptors, CB1 and CB2. Overall, more is known about the CB1 receptor. THC is thought to mediate its psychotropic effects through the CB1 receptor. CB1 was initially cloned from human cells in 1991 [56] and is found in CNS, as well as some peripheral cells. A second receptor was cloned in 1993 from macrophages and spleen, and was termed CB2 [57]. When compared to the CB1 receptor, the CB2 receptor is 68 % homologous in membrane spanning regions and 44 % homologous overall [57]. Both CB1 and CB2 are G-protein coupled, with seven transmembrane spanning regions [58] (Table 3).

The highest density of CB1 receptors in the rodent brain is in the basal ganglia, substantia nigra, globus pallidus, cerebellum, and hippocampus. They are absent in the brainstem [59]. The CB1 receptor inhibits adenylate cyclase activity via Gi/o [60]. Inhibition causes downregulation of cyclic adenosine monophosphate (cAMP), resulting in less accumulation and therefore inhibition of cAMP-dependent protein kinase (PKA). Activation of the CB1 receptor increases mitogen-activated protein (MAP) kinase activity. This mechanism is thought to affect synaptic plasticity, cell migration, and possibly neuronal growth [61]. This receptor modulates calcium conductance through N-and P/Q-type calcium channels and may also increase potassium conductance through an inwardly rectifying potassium channel [62–66]. CB1 expression is particularly dense in presynaptic terminals, and endocannabinoids have been shown to act as retrograde messengers at CNS synapses [60]. CB1 receptors are found on both GABAergic and glutamatergic neurons [61] and are thought to be involved in neurotransmission.

The CB2 receptor was initially thought to only be a peripheral receptor. However, it has now been found throughout the CNS [60], particularly in microglial cells [59]. There is theory that the CB2 receptor is part of a general protective system as part of the immune system [67]. CB2 receptors are found on multiple immune system cells with the amount of mRNA greatest in B cells>natural killer cells>monocytes>polymorphonuclear leukocytes>T cells [68]. Unlike the CB1 receptor, CB2 receptors do not seem to alter the on inward potassium rectifier channels or N or P/Q type calcium channels [69].

Subsequently, multiple different splice variants of the CB1 and CB2 receptors have been found. Receptor variants have been linked to vulnerability to substance abuse in certain populations [70, 71], though the strength of this association is not definitive [72]. It is hypothesized that the association is due to the role of the cannabinoid receptor on the dopamine and cannabinoid reward systems [71]. Research is ongoing to determine the effects of this genetic variation on response to marijuana. For example, Hopfer et al. found that a common CB1 haplotype was associated with fewer cannabis dependence symptoms in adolescents [73].

Synthetic Cannabinoid Agonists

Multiple compounds that bind to cannabinoid receptors have been developed, such as HU-210, nabilone, and dronabinol [74]. Pfizer developed the cyclohexylphenol (CP) series in the 1970s [75]. In 1994, Huffman et al. created multiple different synthetic cannabinoids known as aminoalkylindoles or JWH compounds [74]. These compounds have been identified in the epidemic of novel illicit drug use involving "spice" compounds.

The FDA has approved three synthetic compounds for medicinal use. Nabilone (Cesamet®) was licensed in 1981 and is a schedule II drug (high potential for abuse). It is a synthetic derivative of THC, which is approved to reduce nausea and vomiting associated with chemotherapy [76]. It has been approved in Canada since 1981, but just began being marketed in the USA in 2006. Though it has better efficacy than older antiemetics, no trials have compared it to new antiemetics such as ondansetron. In 1985, dronabinol (Marinol®) was approved as an antiemetic for nausea and vomiting associated with cancer chemotherapy [77]. In 1992, it gained additional marketing approval for appetite stimulation in conditions associated with excessive weight loss such as that occurring in AIDS [78]. The newest drug Sativex® is a combination product of THC and CBD. It was approved in 2005 for management of pain in end-stage cancer patients as well as for pain associated with multiple sclerosis patients [79].

Psychotropic/Neurologic Effects of Cannabis

Common psychotropic effects of marijuana intoxication include induction of a relaxed or dreamy state, loss of time perception, anxiety, and psychosis. Acute, residual, and chronic cognitive effects have been reported.

There is some data that shows that alterations in memory and attention can persist even after acute intoxication has

Table 3 Characteristics of cannabinoid receptors

	CB1	CB2
Receptor type	G-protein coupled	G-protein coupled
Receptor action	Gi/o	Gi/o
Location	Central nervous system (basal ganglia, substantia nigra, globus pallidus, cerebellum, and hippocampus)	Multiple immune cells (B cells, NK cells, monocytes, PMN, T cells)
		Spleen and bone marrow
	Expression particularly dense in presynaptic terminals	Microglial cells of CNS
Effect	Modulation of calcium conductance	Modulation of immune function
	Increased potassium conductance through inwardly rectifying potassium channel	
	Psychotropic effects of cannabinoids	

To date, two cannabinoid receptors have been described with multiple splice variants. The CB1 receptor is thought to be the central receptor responsible for the psychotropic effects of cannabinoids, whereas the CB2 receptor is thought to be a more peripheral receptor with immune modulation effects. Research is ongoing to determine downstream cellular effects of both receptors

resolved. Pope et al. studied heavy cannabis users (>5,000) uses during lifetime and found that they had deficits in memory of word use after a 0-, 1-, and 7-day abstinence period, but by day 28, no significant difference could be found when compared to controls [80]. A separate study examined PET scans during the Iowa Gambling task (a decision making task) and found a difference in brain activity only in heavy users (smoking 53–84 joints/week) when compared to moderate users or controls [81].

A meta-analysis by Crean et al. [82] examined the acute (0–6 h), residual (7 h to 20 days), and persistent (>3 weeks) effects of marijuana use. Overall attention and cognition was impaired acutely in light users, but normal in heavy users. Residual effects were mixed, and long-term attention and cognition was largely normal. Decision making and risk taking were impaired in the residual and persistent time period, but acutely, there were mixed findings. Working memory was impaired acutely, but normalized at the residual and long-term time period.

Despite these adverse effects on memory, attention, and cognition, newer data supports a possible neuroprotective mechanism of cannabinoids in brain injury. This effect seems to be dose related, with lower doses causing injury and higher doses being neuroprotective [83]. One example is the finding that THC inhibits formation of amyloid beta fibrils important in the pathogenesis of Alzheimer's disease [84]. Research is ongoing to determine the effects of THC and synthetic cannabinoids on many neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease [85].

Currently, there is conflicting data on the effect of cannabis on mental illness. There is some evidence that the age of initiation of marijuana predicts the time to onset of mental illness [86–88]. Interestingly, CBD, which does not have any of the psychotropic effects of THC, has been proposed as a potential treatment for schizophrenia and psychosis [89, 90].

Physiologic Effects

Acutely, the physiologic effects of marijuana include tachycardia, bronchodilation, conjunctival irritation, reduced lacrimation, and decreased intraocular pressure [91]. Multiple studies have evaluated the short-term effect of marijuana on bronchodilation. Studies have measured specific airway conductance (sGaw) or forced expiratory volume in 1 s (FEV1) in both asthmatics and non-asthmatics. The majority of studies show increased sGaw or FEV1 in both asthmatics and controls. In general, these effects were significant within 15 min and lasted at least 1 h [92–103]. Marijuana was able to reverse methacholine or exercise-induced bronchospasm [94]. Marijuana has been reported to stimulate respiratory drive in animal models; however, in a study of chronic users, no increases in hypoxic or hypercapnic-induced respiratory drive were noted [97].

The cardiovascular effects of marijuana are likely due to CB2 receptors. Postural hypotension with a reflex tachycardia has been well documented [7]. There has been increased interest in the role of cannabinoids as modulators of cardiac risk after a study showed that TCH inhibited atherosclerotic plaque formation via a CB2 receptor-dependent anti-inflammatory mechanism [104]. Research is continuing to elucidate the role of cannabinoids in ischemia and reperfusion injury.

Respiratory Tract Effects

It is generally accepted that the development of obstructive lung disease and respiratory carcinoma is due to the

compounds in tobacco smoke. Obstructive lung disease is thought to be due to protein and lipid modifications from compounds in the smoke. Bronchogenic carcinoma is thought to be from the mutagenic/carcinogenic effects from compounds such as nitrosamines and benzy(a)pyrene [91]. Given the similarity of marijuana smoke to tobacco smoke, it would logically seem that the effects on the respiratory system would be similar (Table 2).

Much of the early research on marijuana smoke has focused on early pathologic changes, or effects on cell lines. Attempts to extrapolate this data and form definitive conclusions regarding the development of malignancy or obstructive lung disease have produced conflicting data. Research is complicated as marijuana is an illicit substance in most countries and has only been legal for medical use over the past decade; therefore, obtaining accurate longitudinal data is difficult. It seems reasonable to first discuss the data on inflammatory changes on the respiratory tract, as these are believed to precede development of disease processes and then explore the data on specific diseases.

It is important to note that the majority of studies look at either marijuana smoke or users who smoke marijuana in the form of cigarettes. It is possible that different effects could occur from the use of "water pipes" in which the smoke passes through a water chamber prior to being inhaled, or vaporizers in which the plant material is heated to a temperature where THC is released, but smoke is not generated.

Cellular Changes in the Respiratory Tract

Marijuana and tobacco smoking can lead to cytologic changes in the respiratory tract. Evaluation with bronchoscopy in marijuana smokers, compared to smokers of tobacco, versus tobacco and marijuana, and non-smoking controls showed that 91 % of subjects in the smoking groups (32 people) had visible airway hyperemia [105]. Basal cell and goblet cell hyperplasia was more significant in the marijuana group versus the non-smokers. Cellular disorganization was more prevalent in marijuana versus tobacco smokers. Interestingly, squamous metaplasia was found with significantly higher prevalence in the group with concomitant use of marijuana and tobacco than all other groups, leading to a hypothesis that there are additive effects of marijuana and tobacco smoke.

A second study using bronchoscopy found significantly higher bronchitis index scores in marijuana smokers, tobacco smokers, and smokers of both marijuana and tobacco [106]. When biopsies were evaluated, there was a significant increase in the presence of vascular hyperplasia, submucosal edema, inflammatory cell infiltrates, and goblet cell hyperplasia in smokers versus non-smokers.

It is difficult and impossible to study the entire respiratory tract in humans; therefore, a study was performed in rhesus monkeys [107]. Monkeys were exposed to either high-dose (1 joint/day), low-dose (2 joints/week), placebo (one extracted marijuana cigarette 7 days/week), or sham (sham smoke 7 days/week) for 12 months. A 7-month washout period was used, in which animals were not exposed to any smoke, before evaluation of lung tissue. A higher frequency of alveolitis, alveolar cell hyperplasia, and granulomatous inflammation were found in all smoking groups. The marijuana group had a higher incidence of bronchiolitis, bronchiolar squamous metaplasia, and interstitial fibrosis compared to the other smoking groups. Finally, alveolar cell hyperplasia with atypia was only found in the marijuana group. A higher degree of changes was found in the high-dose marijuana group when compared to the low-dose group, which implies dose-related changes.

Bronchoalveolar lavage (BAL) has also been use to characterize cellular changes in smokers. Total number of cells, as grams per milliliter of BAL fluid, was significantly higher in smokers of tobacco, marijuana, and tobacco plus marijuana when compared to non-smokers [108]. In all groups, macrophages were the predominant cell type found. Elevated neutrophil counts were found in all smoking groups, with the highest number in smokers of tobacco plus marijuana. Macrophages, in tobacco or marijuana smokers, were found to have a higher rate of proliferation when compared to non-smokers, which could lead to the higher cell numbers found in BAL fluid of smokers [109]. At this time, the stimulus for cellular proliferation is unknown. Tobacco smokers, unlike marijuana smokers, have significantly lower percentages of CD4 cells, higher levels of CD8 cells, and lower ratios of CD4:CD8 cells in BAL fluid, when compared to non-smoking controls [110].

Marijuana smoke has been found to have multiple effects in cultured cell lines, including increased oxidative stress, suppression of receptor-mediated apoptosis, increase in necrotic cell death, and disruption of mitochondrial function and cellular energetics [111–113]. In an in vitro model using human small airway epithelial cells, THC was found to have a time- and concentration-dependent decrease in mitochondrial membrane potential, ATP level, and cell viability [114]. How these cellular changes translate into disease states remains to be elucidated.

Lung Disease

Given the similarity between tobacco and marijuana smoke, it would stand to reason that smokers of marijuana would be at risk for the same pulmonary complications as tobacco smokers, such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, and asthmatic bronchitis. However, the evidence to show this association is difficult to obtain, as the studies are complicated by a

multitude of factors. First, the concomitant use of tobacco is not controlled for in all studies. Second, the dose of marijuana is difficult to define. Some studies use marijuana cigarette years as duration of exposure, with four to five marijuana cigarettes per day defined as being equivalent to 20 cigarettes per day, whereas other studies use number of times exposed to marijuana. Next, studies have generally been performed on younger patients, which may not allow enough time for pulmonary disease to manifest. In many studies, an attempt is made to control for this limitation by comparing results with tobacco smokers within the same cohort. Finally, outcome measures are not always standardized. With these limitations in mind, the data is reviewed below and summarized in Table 4.

Pulmonary Function

There are studies that have found impairment in respiratory function from marijuana use. An epidemiologic study found small but significant decreases in expiratory flow rate and FEV1/forced vial capacity (FVC) ratio in non-tobacco cigarette smokers when compared to tobacco smokers [115]. When the same group extended research longitudinally, slight decreases were seen in FEV1 and FEV1/forced expiratory volume (FEV) ratio in past smokers of marijuana but not current smokers [116]. One of the limitations of these studies is that they did not quantify marijuana use, and instead used non-tobacco cigarette smokers, with the assumption that this represented marijuana use. An additional cross-sectional study found 36 % of marijuana smokers had a FEV1/FVC ratio <80 %, compared to 20 % of non-smokers [117].

When computerized tomography (CT) was used to evaluate pulmonary parenchymal changes, marijuana use was associated with evidence of hyperinflation, with little evidence of emphysema. In this same group, pulmonary function testing showed evidence of airway obstruction as measured by the FEV1/FVC ratio, though less so than in tobacco smokers [118].

The data supporting a lack of effect of marijuana smoking on pulmonary function is more robust. An observational cohort study showed a decline in FEV1 in male tobacco smokers over an 8-year period, but did not show similar decline in marijuana smokers [119]. A dose-related response was not seen, and there was not an additive effect between marijuana and tobacco smoke. A second cohort study found persistent decrease in FEV1/FVC values over time in marijuana smokers when compared to non-smokers; however, when after adjusting for age, tobacco smoking, and weight, there was no statistically significant difference found [120]. Another study using data from the National Health and Nutrition Examination Survey (NHANES III) found a decrease in FEV1/FVC in marijuana smokers (defined as lifetime use more than 100 times and use at least one in the past month), but when controlling for tobacco use, no difference was found [121].

A recent meta-analysis of 34 studies assessed the impact of short-term and long-term marijuana use. They concluded that there is a short-term bronchodilating effect that is evident soon after smoking. They could not find a consistent association between long-term marijuana smoking and FEV1/FVC ratio, DLCO, or airway hyper-reactivity [122]. Since the publication of the meta-analysis, more studies have been performed.

In a cohort study of 878 people over the age of 40, smokers of tobacco or tobacco plus marijuana were more likely to have respiratory symptoms, and evidence of COPD, as defined by spirometric evidence of a ratio of FEV1 to FVC of less than 0.70 after bronchodilation, than non-smokers [123]. Marijuana smokers were defined as having lifetime use of 50 or more marijuana cigarettes. Marijuana smoking alone did not cause an increase in respiratory symptoms and was not an independent risk factor for development of COPD. Use of marijuana and tobacco together created increased risk of respiratory symptoms and COPD than tobacco alone, suggesting an additive effect. In commentary on this study, Tashkin performed a literature review and concluded that smoking marijuana alone can lead to respiratory symptoms, however, that we can be close to concluding that smoking marijuana alone does not lead to COPD [124]. Another large cohort study of 1,037 patients found that marijuana smokers did have a tendency toward hyperinflation and air trapping, though they did not have evidence of airflow obstruction. Marijuana users were found to have higher FVC levels [125].

A cohort study over a 20-year time period using data from the Coronary Artery Risk Development in Young Adults (CARDIA) data found the expected decrease in FEV1 and FVC in tobacco smokers. However, with low levels of marijuana use, defined as 7 joint-years of life (with 1 joint-year equivalent to 365 joints or filled pipe bowels),

Table 4 Respiratory effects of marijuana smoking

Cellular changes	Airway hyperermia, basal and goblet cell hyperplasia, cellular disorganization, squamous metaplasia
Respiratory symptoms	Cough, wheeze, shortness of breath, sputum production, chest tightness, pharyngitis, hoarse voice, worsening asthma symptoms
Lung function	Hyperinflation, increase/decrease or no change on FEV1, FVC, and FEV. COPD (possible)

there was no adverse effect on pulmonary function. In fact, FEV1 and FVC were actually increased with low levels of exposure. With increasing levels of exposure, FEV1 was not significantly different from baseline, and FVC remained significantly elevated [126]. There are several reports of emphysematous bullous disease in heavy marijuana smokers. The majority of the disease is seen on CT in the upper lobes. Despite CT findings, pulmonary function testing and chest radiographs in these patients tend to be normal [127]. Despite the limitations of the data, a meta-analysis, and the large cohort studies that were published after the meta-analysis, there is evidence for hyperinflation without significant airway obstruction. The clinical relevance of the hyperinflation remains to be determined.

Respiratory Symptoms

Though the evidence for obstructive lung disease is sometimes conflicting, data shows that respiratory symptoms are uniformly increased in marijuana smokers. In the NHANES III study, both marijuana and tobacco smokers had increased likelihood of cough, sputum production, wheezing, chest sounds, and chronic bronchitis [121]. Shortness of breath was increased with tobacco use, but not with marijuana use. Increases in pneumonia were not found with either marijuana or tobacco use. In a longitudinal study, which followed 299 participants, a mean of 9.8 years, current smokers of either tobacco or marijuana were more likely to have symptoms of chronic bronchitis. However, former smokers of either substance were no more likely to have symptoms, showing that cessation of smoking can have clinical benefit [128].

Overall, increases in cough [115, 116, 118, 129], wheeze [115, 116, 118, 129], shortness of breath [115], sputum production [115, 116, 118, 129], chest tightness [117, 118], pharyngitis [130, 131], hoarse voice [131, 132], and worsening asthma symptoms [130, 131] are found in marijuana smokers when compared to non-smokers. Interestingly, one study demonstrated an increase in cough with marijuana smokers (OR, 1.3; CI, 1.0–1.6) and tobacco smokers (OR, 1.4; CI, 1.1–1.9). However, in combined smokers, there was not an association with cough (OR, 1.0; CI, 0.7–1.4) [118].

Neoplastic Effects

Cigarette smoke is a known carcinogen, and given the similarity of marijuana and tobacco smoke, especially with known carcinogens, it would be reasonable to hypothesize that marijuana smoke should be carcinogenic. However, the literature is mixed with regards to the ability of marijuana to cause cancer, and there is some data that synthetic cannabinoids as well as THC have the ability to kill cancer cells. When approaching this data, it is important to evaluate both the effects of marijuana smoke and the effects of cannabinoids alone. A summary of the potential malignant effects of marijuana is summarized in Table 5.

Evidence that marijuana smoke can cause cancer started with findings from the Ames *Salmonella* mutagenesis assay, which is used to determine the ability of compounds to cause cellular mutations. Two studies have demonstrated the ability of marijuana smoke to induce mutations in the Ames assay [9, 24]. When the components of the smoke were further analyzed to determine the causative factors of marijuana smoke, the highest mutagenic potential was found in the basic fraction [133]. The basic fraction of a high-dose marijuana cigarette was found to be sevenfold higher than the base fraction of tobacco smoke. Painting marijuana tar onto mouse skin causes cancerous effects [134]. Though it is unknown how cancerous effects from skin paining on mice correlates to human toxicity, this model is widely accepted as a screening process for the carcinogenicity of chemical compounds including tobacco smoke [135]. In human lung explants, marijuana smoke induces chromosomal and DNA alterations [136]. Furthermore, DNA damage in macrophages has been demonstrated in human marijuana smokers [137]. In contrast to marijuana smoke, THC alone is not carcinogenic in rodent skin tests [138], and is not mutagenic using the Ames test [139].

Carcinogen-DNA adducts are thought to be precursors to the formation of neoplastic cells. In human tissue samples of tobacco smokers, carcinogen-DNA adducts have been found in samples of peripheral lung, urinary bladder, oral mucosa, and placenta [140]. In rhesus monkeys exposed to marijuana smoke for 1 year at either doses of 7 days per week or 2 days per week, there was no increase in carcinogen-DNA adducts found when compared to sham controls [140]. Levels of adducts were higher in animals exposed to ethanol extracted marijuana smoke.

Human epidemiological studies have been mixed with the development of carcinoma. Initial evidence that linked marijuana use with head and neck squamous cell carcinoma (HNSCC) was based on case reports. In a hospital-based case–control study, ever user of marijuana had a 2.6 (CI, 1.1–6.6)-fold increase in HNSCC when compared to blood-bank controls. This association was stronger in people age 55 and younger (OR, 3.1; CI, 1.0–9.7). There was a trend toward increase risk with increasing frequency of use per day and increased years of use [141]. In a North African population, cannabis use had an odds ratio of 2.62 (CI, 1–6.86) for development of nasopharyngeal carcinoma, after attempting to control for tobacco use [142]. However, a potential confounder is that it is common for tobacco to be mixed with marijuana in North Africa. A third study found that human papillomavirus (HPV)-16-positive HNSCC was associated with use of marijuana; however, HPV-16 negative cancer was not [143].

Table 5 Malignancy from marijuana

Ames test: marijuana smoke	Mutagenic
Ames test: THC	Non-mutagenic
Probable increased risk	Non-seminoma germ cell tumors
	Adult-onset glioma
Possible increased risk	Head and neck squamous cell carcinoma
	Lung cancer
	Prostate cancer
	Cervical cancer

See text for details

In contrast, seven studies have been unable to find an association between marijuana use and HNSCC. Two small population-based studies from England, performed by the same group, failed to find an association between cannabis smoking and oral cancer [144, 145]. Another small study, with only 75 cases, also did not find increased risk, but may have been limited by the sample size [146]. Two larger population-based studies did not find increase risk in patients with oral squamous cell carcinoma [147, 148] or esophageal cancer [148]. Using data from the INHANCE consortium, a pooled analysis of 4,085 cases and 5,125 controls was performed. The data from the other two large studies noted above was included in their analysis. An association between marijuana use and head and neck cancer was not found (OR, 0.85; CI, 0.53–1.35) [149]. Finally, a case–control study from Massachusetts found that 10 to 20 years of marijuana use was associated with a decreased risk of HNSCC (OR, 0.38; CI, 0.22–0.67). They concluded that moderate marijuana use is associated with a decreased risk of HNSCC [150].

The evidence for marijuana use contributing to the development of lung cancer is equally divided. A Tunisian case–control study showed a markedly elevated increase risk for lung cancer in marijuana smokers (OR, 8.2; CI, 1.3–15.5). However, the study was small, 110 cases, the duration and frequency of marijuana and tobacco use were not reported, and as noted above, in this region, tobacco and marijuana are often smoked together. A systematic review in 2006 concluded that that there was no data showing an association of marijuana smoking with lung cancer [151]. They did note several limitations to the studies such as lack of adjustment for tobacco smoking, small sample size, selection bias, limited generalizability, and young age, which might give insignificant lag time for the development of malignancy. Since the systematic review, further studies have been performed.

A case–control study of lung cancer patients under 55 showed an increase risk of lung cancer of 8 % (CI, 2–15) for every year of cannabis use [152]. When adjusted for tobacco smoking, this risk only persisted for patients with >10.5 joint/years exposure (RR, 5.7; CI, 1.5–21.6). A second case–control study with 1,212 cases found no increase risk from marijuana smoking, even in patients with >60 joint-years smoking (OR, 0.62; CI, 0.32–1.2) [148]. A review of all prior studies with repeat statistical analysis performed in 2008 found that marijuana was protective for development of lung carcinoma, tobacco smokers were at increased risk, and that smokers of both marijuana and tobacco were at higher risk of developing cancer than marijuana smokers, but lower risk than tobacco smokers [153].

Marijuana smoking has also been associated with the development of other malignancies. In a large cohort study, 64,855 patients were assessed using self-assessment questioners, and followed a mean of 8.6 years. In non-smokers, ever users of marijuana did not have an increased risk of lung, melanoma, prostate, breast, or cervical cancer. In tobacco smokers, ever using marijuana increased the risk of prostate cancer (RR, 2.1; CI, 1.0–9.5) and trended toward risk of cervical cancer (RR, 1.4; CI, 1.0–2.1) [154]. Three small studies have correlated marijuana use with the development of nonseminoma testicular germ cell tumors [155–157]. A large cohort study of 133,811 patients demonstrated an increased risk for malignant primary adult-onset glioma in individuals who smoked marijuana at least once a month (RR, 2.8; CI, 1.3–6.2) [158].

Despite the link between marijuana and development of malignancy, cannabinoids have also been found to have an anti-tumor effect. In a mouse model of lung adenocarcinoma, developed in 1975, oral administration of THC, delta-8-THC, and CBN decreased tumor size and increased survival [159]. Despite this finding many years ago, research on cannabinoids as cancer treatment has only recently been aggressively pursued. Though much of this research has been performed on in vitro models, there is evidence that cannabinoids, including synthetic cannabinoids, could be beneficial in treatment of breast, prostate, and bone cancer [160], as well as glioblastoma multiforme [161].

In summary, marijuana smoke has been shown to cause cellular changes, some of which are concerning as possible precursors to malignant changes. The development of carcinoma has been difficult to definitively prove in human epidemiological studies. There are limitations to these studies, which include underreporting due to marijuana's illegal status, confounders such as concurrent tobacco, ethanol, or

other drug use, as well as time, as cancer takes years to develop, and many participants in these studies were young. Therefore, more research is needed on this complex subject before a final determination can be made.

Immune System Effects

The effects of cannabinoids on the immune system are dependent on the specific cannabinoid studied, cell lines used, and dose given. Though CB1 and CB2 receptors are both expressed on immune system, CB2 receptors are expressed in a much higher level. When looking at the distribution of CB2 mRNA, the levels are greatest in B cells>NK≫monocytes>PMNs>T8 cells>T4 cells [162]. The exact mechanism through which exogenous and endogenous cannabinoids upregulate and downregulate immune function is a subject of continued investigation. The effect of cannabinoids on immune function has been extensively reviewed in two articles [163, 164]; therefore, an overview of effects on immune cells will be provided below.

Lymphocyte Effects

In humans, the effect of marijuana on T cell proliferation has been shown to have no effect [165, 166] or has demonstrated decrease in sensitivity [167]. A study of patients who ingested marijuana over 6 to 36 months showed a decrease in the number of T and B cell lymphocytes when compared to controls [168]. However, other studies have shown no difference in the number of T and B cell lymphocytes in chronic marijuana smokers [169]. Overall, there is evidence of a biphasic response of both T and B cell lymphocytes to cannabinoids, where low doses seem to simulate cells and high doses tend to decrease numbers of lymphocytes [163]. In a recent randomized, placebo-controlled trial of HIV-positive patients randomly assigned to marijuana cigarette, dronabinol capsule, or placebo, viral load decreased, and there was not an effect on CD4+ or CD8+ cells for both marijuana cigarette and dronabinol capsule groups when compared to placebo [170]. In a rat model, injected CBD decreased total leukocyte numbers [171].

Macrophage Effects

THC has been shown to have multiple effects on macrophage function including phagocytic ingestion, spreading, oxidative burst, protein expression, DNA synthesis, cytolysis, arachidonic acid release, and antigen presentation [164]. In alveolar macrophages isolated from rhesus monkeys chronically exposed to marijuana smoke, morphologic changes and alterations in protein expression were seen, after a 7-month period without exposure [172]. Alveolar macrophages from human smokers of marijuana showed decreased antimicrobial activity, which was thought to be due to decreased production of nitric oxide [173].

Natural Killer Cell Effects

In the presence of THC, natural killer (NK) cells show diminished production of tumor necrosis factor alpha (TNF-α) when challenged with *Candida albicans* [174]. In vitro, natural killer cells have decreased antitumor activity when exposed to THC [174–176]. In a murine model, THC significantly inhibited NK cell activity [177]. CBD did not have effects on NK cells in a rat model [171].

Neutrophil Effects

There is not data on the effect of THC on the polymorphonuclear leukocyte line. Cannabinoid receptors have not been found on the neutrophil surface, and therefore, it is unlikely that THC exhibits direct effect on neutrophils.

Effects on Cytokine Production

Cytokines are important mediators in host response to infection. In macrophages, THC has been shown to cause impaired tumor necrosis factor alpha (TNF-α) release and enhance interleukin 1 (IL-1) secretion [178–181]. In mouse splenocyte cultures exposed to THC, or mice injected with THC, interferon (INF) production is reduced [182]. INF-α/β production was reduced in a mouse model where mice were injected with THC and subsequently infected with the human simplex virus [183]. Finally, IL-2 production is suppressed after exposure to THC. The mechanism of IL-2 reduction appears to be decreased protein synthesis of IL-2 receptor proteins with subsequent downregulation of IL-2 receptors [184].

Other Effects

Barotrauma

Case reports and case series describe young patients with predominately upper lobe bullous disease leading to complications such as pneumothorax [185, 186]. This has been termed marijuana lung [187] or “bong lung” [188]. Smokers of marijuana tend to differ from those of other substances, in that they inhale more deeply and hold the smoke in their lungs, performing a Valsalva maneuver. These techniques may put marijuana smokers at increased risk for bleb rupture, leading to pneumothorax or pneumomediastinum. Pneumorachis (air in the spinal canal) and pneumomediastinum have also been reported after marijuana smoking from a homemade apparatus

[189], and pneumomediastinum has been reported after alternate use of cocaine and marijuana [190].

Aspergillus Infection

Aspergillus fumigatus spores can contaminate marijuana. In one study, precipitins to *Aspergillus* were detected in 11 of 21 marijuana smokers tested [191]. The development of chronic pulmonary aspergillosis (CPA) has been associated with marijuana use in patients on chemotherapy, with leukemia, renal transplant, and acquired immunodeficiency syndrome (AIDS) [192]. The development of CPA in marijuana smokers is uncommon, and most case reports are in patients with underlying immunodeficiency. One immunocompetent habitual marijuana smoker developed invasive aspergillosis involving the sphenoid sinus [193]. It is unclear if the *Aspergillus* infection is due to the handling of the marijuana or from actually smoking.

Summary and Conclusions

Cannabinoids have multiple effects on the pulmonary system, immune system, and on cancer cells. Daily marijuana smoking has been shown to increase the risk for pulmonary symptoms such as wheeze, cough, and sputum production, though the risk for development of COPD is questionable. It is difficult to differentiate the effects of individual cannabinoids with the effect of marijuana smoke.

Though laboratory data has demonstrated the mutagenic and carcinogenic properties of marijuana smoke, human epidemiologic studies have been equivocal in finding a link between marijuana and cancer. However, it also took time to determine the causality of tobacco in the development of malignancy. New evidence shows that cannabinoids may have some cancer fighting properties. Further longitudinal studies are needed to continue to examine the effects of cannabinoids on malignancy.

The effect of cannabinoids on the immune system is unclear. Overall, it appears that THC has a depressant effect, which could lead to increased susceptibility to infection. Research is demonstrating that the immunomodulatory properties of cannabinoids may have clinical use in the treatment in autoimmune diseases.

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