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A Systematic Review of the Respiratory Effects of Inhalational Marijuana

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This systematic review focuses on respiratory effects of inhalational marijuana. The systematic review of the literature was conducted using a comparative method between 2 researchers. Abstracts were reviewed for inclusion of respiratory effects related to inhalational marijuana. Relevant abstracts were collected, and full text articles were retrieved for review. Articles were removed if they did not contain burning marijuana; were animal studies; or were editorials, systematic reviews, commentaries, non-English language, or non-respiratory-related articles. Forty-eight articles were collected and categorized by respiratory effects. In particular, lung cancer, bullous emphysema/COPD, and other respiratory symptoms were the primary categories. Articles were noted by study population country, sample size, age distribution, and findings that were pertinent to respiratory health. The research indicates that there is a risk of lung cancer from inhalational marijuana as well as an association between inhalational marijuana and spontaneous pneumothorax, bullous emphysema, or COPD. A variety of symptoms have been reported by inhalational marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation, and other symptoms. It is important to stay current with research findings to educate patients on this smoking behavior. *Key words: cannabis; marijuana; inhalational; respiratory; symptoms.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Cannabis (marijuana) is the most commonly used drug in the United States and abroad. Marijuana consists of the dried leaves and flowers of the *Cannabis sativa* plant. Because of environmental influences on plant growth, chemical potency varies.[1] Over 60 cannabinoids and 400 compounds have been identified in marijuana.[2] Most common among these cannabinoids is THC (1-δ-9-tetrahydrocannabinol), which is believed to be the primary cannabinoid responsible for the psychoactive effects produced from consumption. The primary differences between marijuana smoke and cigarette smoke are the cannabinoids in marijuana and the nicotine in cigarette smoke. Nicotine is known to be the addictive substance of cigarette smoking. With the illicit nature of marijuana, less research has been conducted on the constituents of the smoke and on the respiratory effects of inhalational marijuana. However, both contain cancer-causing nitrosamines, polycyclic aromatic hydrocarbons, vinyl chlorides, and phenol.[3]

Before the Marijuana Tax Act of 1937, cannabis was used medicinally, and in 1970, it was classified as a Schedule 1 drug due to the potential for abuse, lack of acceptance as medical treatment, and lack of safety.[4] Other drugs in the Schedule 1 category include heroin, ecstasy, and lysergic acid diethylamide (LSD).[5] Over the past several years, legalization of recreational cannabis has occurred in 4 states and the District of Columbia, which will help to propel and allow more research on this formerly illicit drug.[6] The use of cannabis has steadily increased over the years, with current past month users estimated at 19.8 million people.[7] Adolescent use and perception has remained stable in recent years according to the National Institutes of Health.[8] Nearly 64% of high school seniors in 2014 viewed cannabis as being not harmful compared with 35% in 1994.

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Table 1. Search Terms and Databases

Databases	Terms
PubMed	Advanced term "Marijuana"
OVID	Marijuana smoking and respiratory system
	Cannabis: adverse effects
	Marijuana smoking: epidemiology
Web of Science	Marijuana smoking/epidemiology
	Cannabis/adverse effects*
	Marijuana smoking/epidemiology*
	Marijuana smoking/physiopathology
	Lung diseases/chemically induced
	Marijuana smoking/adverse effects*
	Respiratory system/drug effects*
	Marijuana abuse/respiratory complications

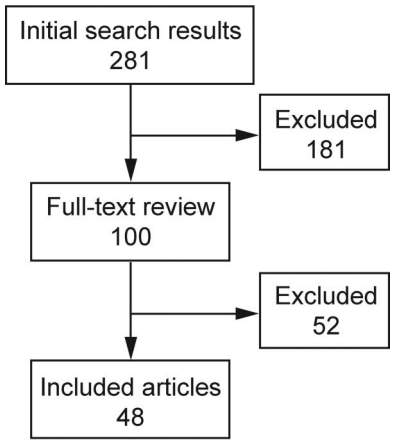

Fig. 1. Flow chart.

The widespread use of marijuana has raised concerns for medical practitioners regarding the long-term respiratory effects. Most research has considered mental health effects, but research on respiratory effects has not been explored recently. Our systematic review of the literature serves to describe what empirical literature exists on the respiratory effects of inhalational cannabis, in particular. Although cannabis is consumed in various forms, our research study and comprehensive literature review was particularly focused on the inhalational effects to better serve as a comprehensive guide for respiratory therapists, pulmonologists, and others in the health-care field.

Review of the Literature

Search Strategies

Inhalational marijuana peer-reviewed articles published from 1967 to 2015 were identified from the PubMed, OVID, and Web of Science databases using the search terms shown in Table 1. Retrieval of the peer-reviewed articles was performed by 2 researchers (JBM and AM). The initial review commenced with an abstract review to exclude any commentary letters, reviews, editorials, non-English language studies, and animal studies (ie, non-research studies applicable to respiratory, synthetic marijuana, and medical cannabis). Additionally, the reviewers restricted the search to inhalational marijuana only and were focused only on its respiratory health effects.

The search term "lung diseases/chemically induced" revealed 27,220 abstracts. An advanced search on "lung diseases/chemically induced" was conducted using the term "marijuana" and resulted in one abstract therefore, similar search with term "respiratory system/drug effects*" yielded 2,548 abstracts. Abstracts that could not be categorized based on the lack of information provided in the abstract were reviewed in full text form to allow a final decision regarding classification.

We identified 281 abstracts (250 from PubMed, 2 from OVID, and 29 from Web of Science) through the literature search, as noted in Figure 1. Omitted abstracts included any duplicates, systematic reviews, editorials, commentaries, non-English language articles, animal studies, unattainable full text articles, or those that were not inclusive of respiratory health. An additional 19 unidentified abstracts were listed but provided no direct access to the full text. Of these, 100 articles were reviewed for inclusion. Fifty-two were removed for lack of fit with the inclusion criteria. The final 48 articles were included in this systematic review.

After review of the articles, we developed a matrix to delineate articles by date of publication, study design, study population and country, age of study participants, and findings deemed important to respiratory health. Furthermore, the studies were organized into tables by disease. Table 2 indicates studies that primarily addressed lung cancer; Table 3 describes studies related to bullous emphysema, COPD, or pneumothorax; and Table 4 categorizes studies that reflected various respiratory-related symptoms or findings in cannabis smokers.

Results

Our synthesis of the data represents a more current literature review on the inhalational health effects of marijuana use and other risk factors.[57-60] Our findings are consistent with other systematic reviews that confirm studies indicating that marijuana use poses negative respiratory effects in smokers.[12,16,61] Our study categorizes the literature by study type and generalized findings helpful for health-care professionals.

Regarding lung cancer risk, 12 studies were retrieved from the systematic review and are noted in Table 2. Of these studies, 4 were case-control studies,[9,11,15,20] one was an experimental study,[10] 4 were secondary data analyses

Table 2. Lung Cancer and Inhalational Marijuana

Study Design	Author (Year)	Study Population	Sample Size, N	Age, y	Findings
Case-control	Aldington et al (2008)[9]	New Zealand males and females	403 (79 cases/324 controls)	35–55	Risk of lung cancer increased 8% (2–15%) for each joint-year of cannabis smoked. Adjusted for confounding variables, including cigarette smoking.
Experimental bronchoscopy for mucosal specimens	Barsky et al (1998)[10]	United States males and females	104 (28 nonsmokers/76 smokers)	21–50	Marijuana-only smokers had greater associations than tobacco-only smokers for basal cell hyperplasia, nuclear variations, and cell disorganization.
Case-control pooled study	Berthiller et al (2008)[11]	Tunisian, Moroccan, and Algerian males	1,208 (430 cases/778 controls)	ND	All marijuana smokers were cannabis smokers. A 2.3-fold increase in risk of lung cancer for ever-cannabis users after adjusting for lifetime tobacco pack-years.
Population-based cohort study	Callaghan et al (2013)[12]	Swedish males in military	49,321	18–21	Heavy cannabis use was significantly associated with a 2.12 association of lung cancer risk after adjusting for baseline tobacco use and respiratory conditions.
Secondary data analysis of prospective cohort study	Chen et al (2008)[13]	United States males and females	64,855	15–49	Lower probability of lung cancer among male and female cannabis-only smokers compared with tobacco-only smokers.
Case report	Graef et al (2011)[14]	United Kingdom male	1	26	Cannabis-only smoker complained of chest pain, weight loss, and facial swelling. The report indicates small cell lung carcinoma in one individual.
Case-control (population)	Hashibe et al (2006)[15]	United States males and females	1,212 incident cancer cases/ 1,040 cancer-free controls	18–65	Using marijuana for >30 joint-years was positively associated with oral, lung, and esophageal cancer, but no positive association was noted when adjusting for cigarette smoking.
Birth cohort study	Jemal et al (2001)[16]	United States males and females	ND	24–83	Birth cohort lung cancer mortality after 1950 reflects teenage cigarette smoking initiation with a contribution from marijuana smoking.
Case report	Kothadia et al (2012)[17]	United States male	1 marijuana-only smoker	22	Association between cannabis smoking and increase in lung cancer in cannabis smoker.
Retrospective cohort study	Sidney et al (1997)[18]	United States males and females	64,855	15–49	Compared with nonusers/experimenters, current use of marijuana was not associated with increased risk of cancer. When adjusting for cigarette smoking, marijuana was not associated with tobacco-related cancers.
Retrospective analysis	Taylor et al (1998)[19]	United States males and females	10	Age < 40 with diagnosis of respiratory carcinoma	Six of the 10 cancer subjects were also tobacco users. Carcinogenic factors are involved in this case series.
Hospital-based case-control	Voirin et al (2006)[20]	Tunisian men	337 (149 cases/188 controls)	ND	Increased risk ratio of lung cancer by 4.1 (4.1, [95.1; CI 1.9–9.0]) after adjusting for tobacco use and occupational exposures.
Secondary data analysis	Zhang et al (2015)[21]	United States, Canada, United Kingdom, and New Zealand males and females	5,144	ND	Weak association between cannabis and lung cancer in subjects who were never tobacco smokers.

ND = no data

Table 3. Bullous Emphysema, Pneumothorax, and COPD Articles Associated With Inhalational Marijuana

Study Design	Author (Year)	Study Population	Sample Size, N	Age, y	Findings
Retrospective study matched for same pathology-spontaneous pneumothorax	Fiorelli et al (2013)[22]	Italian males	153 marijuana smokers/140 nonsmokers	21–54	Incidence of lung bullae higher in cannabis smokers <35 y old ($P < .05$).
Population-based cohort study	Hancox et al (2010)[23]	New Zealand males and females	1,037	18–32	Cannabis use associated with higher lung volumes ($P < .001$), suggesting hyperinflation and increased large airway ($P < .005$) resistance. Limited evidence for airflow obstruction or impairment of gas transfer.
Case report	Hazourad et al (2001)[24]	French male	1	19	Pneumomediastinum emphysematous changes noted in patient.
Case series	Hii et al (2008)[25]	Australian males and females	10	32–50	Asymmetrical bullae in upper to middle zones in patient.
Case study	Jay et al (2011)[26]	United States male	1	58	Patient with large left lung bullae experiencing hemoptysis and pleuritic chest pain. Patient smoked cannabis and crack cocaine; $FEV_1/FVC = 0.73$.
Case series	Johnson et al (2000)[27]	United Kingdom males	4	27–46	Bulla formation in several patients. Indication of the differences in alveolar macrophage activity. Combination of direct pulmonary toxicity together with pleural pressure swings and airway barotrauma associate with high inspiratory flow in cannabis smoking.
Cross-sectional study	Macleod et al (2015)[28]	United Kingdom males and females	500	>18	Increased prevalence of cough ($P < .02$), phlegm ($P < .001$), and wheeze ($P < .001$). The study suggests that COPD should be considered in younger patients who smoke cannabis.
Case series	Morris et al (1985)[29]	United States males and females	13	15–40	Autopsies of cannabis smokers with sudden death identified random sections of lung tissue revealing accelerated pathologic changes leading to pulmonary scarring, emphysema, and eventual COPD.
Cohort study	Rooke et al (2013)[30]	Australian	350	<40	No significant difference between cannabis only and cannabis and tobacco combined in terms of COPD.
Cross-sectional spirometry and self-report study	Tan et al (2009)[31]	Canadian males and females	856	≥40	Compared with nonsmokers, cannabis smokers had 1.66 greater odds of COPD defined by spirometry; 1.66 (0.52–5.26), 95% CI and decreased odds by 62 (0.31–1.27) for self-reported symptoms.
Case study	Van Landeghem et al (2012)[32]	Belgian male	1	33	Emphysematous bullae noted in apices.

Table 4. Other Respiratory Symptoms and Inhalational Marijuana

Study Design	Author (Year)	Study Population	Sample Size, N	Age, y	Findings
Cross-sectional	Aldington et al (2007)[33]	New Zealand males and females	339	18–75	Wheeze associated with cannabis OR 1.3 (1.0–1.6), chest tightness OR 1.4 (1.1–1.7), cough OR 1.5 (1.1–2.0).
Cohort study	Bloom et al (1987)[34]	United States males and females	990	15–40	Phlegm, wheeze, and shortness of breath statistically significant ($P < .005$). No significant effect on lung function in females and males. Significant $\dot{V}_{max75}$ in females. Significant FEV_1/FVC ($P < .05$) in males.
Case study	Cescon et al (2008)[35]	Canadian male	1	65	History of cannabis use. Patient presents with an invasive aspergillosis cause of cavitary lung disease.
Cohort study	Gil et al (1995)[36]	United States males and females	33	35–39	Habitual cannabis smoking has a modest effect on alveolar permeability, suggesting smaller degree of lung injury compared with traditional cigarette smoking.
Case studies	Gilbert et al (2013)[37]		2	20,27	Tainted marijuana case studies. Patients progressed with hypoxemic respiratory failure.
Experimental bronchial isolate retrieval	Grassin-Deyle et al (2014)[38]	French males and females	88	45–84	Explanatory acute bronchodilation produced by cannabis smoking. Activation of CB1 receptors mediates the inhibition of Electrical Field Stimulation-evoked cholinergic contraction in human bronchus.
Secondary analysis cross-sectional	Hublet et al (2007)[39]	Denmark, Belgium, Canada, Finland, France, and Netherlands asthmatic/non-asthmatic students	1,516 non-asthmatic daily smokers/259 asthmatic daily smokers	15	Adolescent asthma patients are more likely to experience wheezing and nocturnal cough ($P < .001$) than adolescents without asthma.
Case report	Liebling et al (2013)[40]	United States male	1	60	The mechanism for eosinophilic pneumonia reported is cannabis-induced.
Cross-sectional study	Moolchan et al (2005)[41]	United States females	37	14–16	The blunt use was associated with CO ≥ 8 ppm, compared with non-blunt occasions. Blunt cannabis use had increased CO levels compared with blunt without cannabis (P = .013).
Secondary data analysis of cohort study	Moore et al (2004)[42]	United States males and females	6,728	20–59	Cannabis use associated with chronic bronchodilation $P = .02$, cough $P = .001$, phlegm $P < .001$, and wheeze $P < .001$.
Case series	Nguyen et al (2010)[43]	French males	3	28–48	Cannabis smokers are at an increased risk of legionnaires disease.
Case-control study	Oeltmann et al (2006)[44]	United States males	11	ND	Patients' behavior of smoking cannabis in a closed car; "hotboxing." Indication of transmission for *Mycobacterium tuberculosis*.
Secondary data analysis of longitudinal study	Pletcher et al (2012)[45]	United States males and females	5,115	18–30	Occasional cannabis use may not be associated with adverse consequences on pulmonary function.
Cohort study	Roth et al (1988)[46]	United States males and females	48	20–49	Habitual smoking of cannabis and/or tobacco produces airway inflammation. No correlation noted between the presence symptoms and abnormal spirometry results.

(*continued*)

Table 4. Continued

Study Design	Author (Year)	Study Population	Sample Size, N	Age, y	Findings
Secondary analysis	Roth et al (2004)[47]	ND	ND	ND	Studies associating cannabis and cocaine with an increase in opportunistic infections, susceptibility to HIV infection, and possible progression of AIDS.
Case study	Sakkour et al (2008)[48]	United States female	1	56	Diagnosis invasive pulmonary aspergillosis. Patient history of COPD.
Case report	Scheel et al (2012)[49]	German male	1	29	Patient with history of fever dyspnea and cervical emphysema. Examination indicates chronic interstitial lung disease caused by talcum-adulterated cannabis.
Experimental bronchoalveolar lavage	Sherman et al (1991)[50]	United States males and females	63	24–55	Cannabis smokers do not produce an increased amount of oxidants when compared with nonsmokers.
Experimental pulmonary function test study	Tashkin et al (1973)[51]	United States males	32	21–30	Significant increase in specific airway conductance to the $P < .05$.
Experimental pulmonary function test study	Tashkin et al (1980)[52]	United States males and females	74	ND	Airway resistance and thoracic gas volume were significantly higher with $P < .01$. The specific conductance values were significantly lower in marijuana smokers compared with nonsmokers.
Cross-sectional questionnaire and lung function tests	Tashkin et al (1987)[53]	United States males	279	25–49	Airway conductance and airway resistance worsen among male cannabis users.
Cross-sectional questionnaire and spirometry	Taylor et al (2000)54	New Zealand young adults	943	21	Respiratory changes with cannabis use included early morning sputum production, wheeze, exercise-induced shortness of breath, and chest tightness.
Experimental bronchoalveolar lavage peripheral blood sample study	Wallace et al (1994)[55]	United States males and females	46	ND	Tobacco and cannabis have effects on bronchoalveolar and peripheral blood T-lymphocytic subpopulations in type or magnitude.
Case study	Zarfin et al (2012)[56]	Infant	1	13 months	Secondhand cannabis smoke is toxic to infants. Infant presented with altered state of consciousness.

OR = odds ratio
ND = no data
CB1 = cannabinoid receptor type 1
EFS = electrical field stimulation
HIV = human immunodeficiency virus
AIDS = acquired immune deficiency syndrome

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of cohort studies,[12,13,16,18,21] one was a secondary data analysis of pathology reports,[19] and 2 were case reports.[14,17] Seven of the studies involved United States participants; one study was based out of New Zealand; one was based out of the United Kingdom; one was a pooled cohort from Tunisia, Morocco, and Algeria; one study involved Swedish military personnel; one study involved a cohort of Australian adults; and a final study was based solely on Tunisian males. The majority of the studies involved male and female adults. Eight of the studies indicated an increased risk of lung cancer from cannabis use or cases indicating lung cancer occurrence,[9-12,14,16,17,19,20] and 4 studies found either no significant association or a lower risk for lung cancer.[13,15,18,21] Some of the studies controlled for the effects of tobacco smoking in the data analysis. Of those that found an association, the risk range varied from 2.1- to 4.1-fold increased risk.

Our findings on lung bullae formation indicate research primarily involving case study reports with small sample sizes and 5 studies of larger sample size. Lung bullae were noted in 5 of the cases, as seen in Table 3. The bullae were noted in the middle to upper lung fields, with one mediastinum case.[22,25,27,32,26] One subject was diagnosed with a pneumomediastinum upon review of symptoms and x-ray.[24] Use of the bong for cannabis smoking is suggested as probably prompting the pneumomediastinum. Fiorelli et al[22] conducted a matched study based on pneumothorax pathology and ascertained that of the study sample, younger smokers age <35 y were more likely to exhibit lung bullae.

COPD, emphysema, and lung hyperinflation were also noted in marijuana smokers.[23,24,28-31] In particular, a study by Tan et al[31] assessed self-symptoms and spirometry in a sample of >800 Canadian males and females to indicate a relationship between COPD and inhalational marijuana. Hancox et al[23] published a population-based cohort study and did not find enough evidence for air flow obstruction but did indicate that hyperinflation is related to inhalational marijuana.

Other respiratory symptoms, infectious disease transmission, and altered pulmonary effects were noted in many of the studies found in Table 4. Five studies indicated symptoms such as wheeze, shortness of breath, phlegm production, and/or chest tightness.[33,34,39,42,49,54] In contrast, 2 studies indicated bronchodilatory effects from inhalational marijuana.[38,42] From a pulmonary function standpoint, one study found a significant $\dot{V}_{max75}$ in females and a significant FEV_1/FVC in males.[34] Studies by Pletcher et al[45] and Roth et al[46] found no abnormal spirometry. One author found significant increases in specific airway conductance,[51] whereas a later study found specific airway resistance to be lower in marijuana smokers compared with nonsmokers.[52] In a later study, the same author found airway conductance and airway resistance to be worsen in male cannabis users.[53]

Aspergillosis, legionnaires, tuberculosis, opportunistic infections, and eosinophilic pneumonia were noted in several studies, probably due to the device harboring opportunistic infectious agents that are inhaled into the respiratory system.[35,40,43,44,47,48] Several of the bacterial transmission had been found in other shared smoking devices, such as hookah smoking pipes. One study found through bronchoalveolar lavage that the bronchoalveolar effects of cannabis on lymphocytic subpopulations increased in magnitude,[55] and a contrasting study found smaller degrees of lung injury as compared with traditional cigarette smoking.[36]

Another respiratory effect involved carbon monoxide levels that were assessed with smoking cessation subjects indicating slightly higher CO levels with blunt use compared with non-cannabis users.[41] There was no evidence of increased oxidants in cannabis users as compared with nonsmokers.[50] The secondhand effects of marijuana smoke were evidenced in a case where an infant was exposed to the smoke and experienced altered state of consciousness, indicating that smoking can be toxic around infants.[56] Tainted marijuana resulted in acute respiratory failure in 2 case reports.[37]

Conclusions

Although much is known about tobacco smoke, less is known about marijuana smoke, and inferences cannot be made about one based on the other. Both types of smoke contain particulate matter and carcinogens; however, it has been reported that marijuana components may minimize some carcinogenic effects.[62] The particulate matter has an inflammatory response effect on the pulmonary system. There is some evidence in large studies to indicate that inhalational marijuana has adverse effects on the respiratory system[22,25,28,31,34,53] and, conversely, bronchodilatory effects.[42] More evidence is needed to support or refute these claims. In particular, direct relationships need to be formulated to avoid confounders in making cause/effect claims. With increasing usage and legalization of marijuana, more research will surface and serve to validate or refute current studies that are presented. Clearly, there are limitations in some of these studies based on self-reporting and also with subjects who smoke cigarettes alongside of their marijuana behavior. It is difficult to make claims of cause and effect with known effects of traditional cigarette smoking confounding some studies. Despite the limited research and limitations in the research on inhalational marijuana, the evidence provided does serve to educate respiratory therapists, pulmonologists, or other health-care professionals and provide knowledge of evidence-based

research that can be shared with subjects who currently smoke cannabis.

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