

The highs and lows of marijuana use in allergy



Nathan Rabinovitch, MD, MPH ^{*,†}; Donald Y.M. Leung, MD, PhD ^{*,†}; Ronina Covar, MD ^{*,†}

^{*} Department of Pediatrics, National Jewish Health, Denver, Colorado

[†] Department of Pediatrics, University of Colorado at Denver Health Sciences Center, Aurora, Colorado

ARTICLE INFO

Article history:

Received for publication January 16, 2018.

Received in revised form February 2, 2018.

Accepted for publication February 5, 2018.

Introduction

In November 2012, Colorado and Washington became the first states to pass initiatives legalizing marijuana use. Since then, voters in 8 states and the District of Columbia have passed similar legislation, and Vermont recently announced plans to do so. It is likely that this trend will continue because marijuana sales in legalizing states have added significant revenue to their state economies. This rapid expansion highlights the need for studies that measure health effects of marijuana use in the population. Because this change is relatively new, many clinicians are likely unaware of the potential health effects of marijuana use and how increasing prevalence may affect what they see in their asthma and allergy practices. We start with a case that features serious complications of marijuana use in asthma.

Clinical Vignette

M.P.D. is a 19-year-old male with a history of asthma since 1 year of age, with uncontrolled disease since age 10 requiring multiple hospitalizations and systemic steroid courses, approximately 2 to 3 times a year. The patient has a history of poor medication adherence, often running out of controller medication (high-dose inhaled corticosteroid and a long-acting β -agonist). He has either smoked marijuana through a bong or used marijuana edibles, several times a week, primarily for relaxation, as he suffers from anxiety symptoms. He denies smoking cigarettes. He lives in an apartment unit with his girlfriend, who also smokes marijuana. Over a weekend, M.P.D. was smoking marijuana daily, a few times a day. That Sunday night, he suddenly started feeling poorly, with nasal congestion, sore throat, productive cough, and subjective feeling of fever. He also complained of chest pain and tightness with every breath, unlike anything he had experienced in the past. He started

using his albuterol rescue inhaler without much relief; hence, he came to the urgent care at National Jewish Health. M.P.D.'s vital signs were: blood pressure 114/63 mm Hg; heart rate 118/min; respiration rate 20/min; and oxygen saturation 89% to 91%. On examination, he was in mild respiratory distress and looked fatigued. He had posterior pharyngeal wall erythema and erythematous, swollen inferior turbinates. He did not have neck or chest wall crepitus, but had tender cervical lymphadenopathy. Breath sounds were diminished with diffuse inspiratory and expiratory wheezing and a prolonged expiratory phase, without crackles or retractions. Initial spirometry showed forced vital capacity (FVC) 1.82 L (40% of predicted), forced expiratory volume in 1 second (FEV₁) 0.63 L (19% of predicted), and FEV₁/FVC ratio 35, and his expiratory flow volume loop was almost completely flattened. After 3 nebulized treatments with combined albuterol sulfate/ipratropium bromide, FEV₁ reversed only slightly. A portable chest radiograph showed no evidence for pneumonia, but, due to limitations of respiratory motion, an air leak could not be excluded. He underwent a noncontrast chest computed tomography scan, which showed a pneumo-mediastinum, neck and chest wall emphysema, diffuse bronchial wall thickening, air trapping, and near-complete right middle lobe atelectasis (Fig 1). A complete blood count was notable for 91% neutrophils. Sputum examination demonstrated 100% segmented neutrophils with normal respiratory flora, and respiratory viral polymerase chain reaction test was positive for rhinovirus. The patient was admitted for 5 days on oxygen supplement, continuous albuterol nebulized treatments for over 48 hours before weaning, and prednisone therapy. Additional lung function tests and airway clearance interventions were held. Behavioral counseling was initiated. Four weeks after discharge, his FEV₁ was back at 90% predicted and chest x-ray film demonstrated resolution of pneumo-mediastinum and atelectasis.

Prevalence of Marijuana Use

As part of the legislation that legalized marijuana use in January 2014, the Colorado Department of Health and Environment was

Reprints: Nathan Rabinovitch, MD, MPH, National Jewish Health, 1400 Jackson Street, Denver, CO 80206; E-mail: rabinovitchn@njhealth.org.

Disclosures: Authors have nothing to disclose.

<https://doi.org/10.1016/j.anaai.2018.02.011>

1081-1206/© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

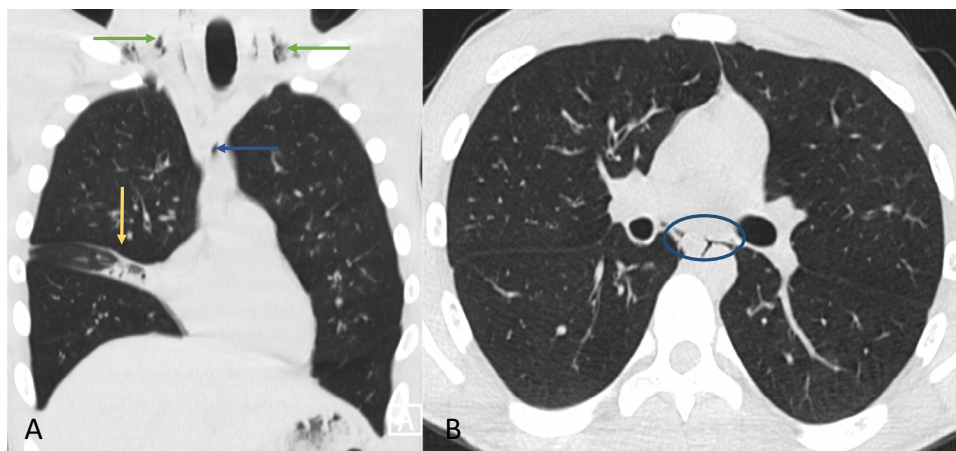


Figure 1. (A) Chest computed tomography scan without contrast showing subcutaneous emphysema in the cervical area (indicated by green arrows), pneumomediastinum (indicated by blue arrow), as well as atelectasis in the right middle lobe (yellow arrow). (B) Sagittal section demonstrating pneumomediastinum around the esophagus and the aorta.

mandated to study the potential health effects of marijuana use.¹ Results of telephone surveys performed in 2014–2015 estimated that 13% of Colorado adults used marijuana in the previous month as compared with a reported national average of 8% use, with young adults aged 18 to 25 reporting the highest usage at 26% (national average 21%).² Concurrent with these high prevalence rates, marijuana-related health effects in Colorado appear to be rising. Among 18- to 25-year-olds, approximately 8% of hospitalizations and 2% of emergency department visits had a marijuana-related billing code (compared with 3% and <1%, respectively, before 2015). Calls to the poison center for marijuana-related poisonings in children have also increased.³ Some of these changes may reflect increased awareness among physicians; however, overall, the trends are concerning and suggest that marijuana use is becoming an increasing public health hazard. In this Perspective, we describe some of the potential health effects that allergists should be aware of.

Respiratory Health Effects

Based on Colorado data, much of the marijuana usage is smoking-related (almost 80% of users report smoking, 31% vaping, and 33% edible ingestion).¹ The available data regarding respiratory effects are almost exclusively related to active smoking, but little is presently known about the effects of second- and third-hand marijuana smoke exposure. Because 40%–50% of tetrahydrocannabinol (THC) content in marijuana cigarettes is released as side stream smoke,⁴ the significant effects presumably can occur with passive exposure as they do with second-hand exposure to tobacco smoke. In this context, a reported 6% of pregnant mothers in Colorado reported smoking marijuana within the previous month (compared with the 3.9% national average⁵) and it is estimated that, in approximately 16,000 Colorado homes, children 1 to 14 years of age are exposed to second-hand marijuana smoke or vapor.¹

Intuitively, one should expect health effects from marijuana smoke to be similar to the well-described effects of tobacco smoke. With the exception of the active ingredients (cannabinoids for marijuana, nicotine for tobacco smoke), studies have shown that the pyrolyzation of both marijuana and tobacco results in smoke with similar components.⁶ Both tobacco and marijuana smoke contain reactive oxygen species, and various polycyclic aromatic hydrocarbons, which are thought to play a role in worsening asthma from tobacco smoke and other combustible products such as ambient air pollution. On bronchoscopy, smokers of tobacco and marijuana demonstrate similar immunologic and histopathologic changes in the

tracheobronchial tree, such as increased broncheolaveolar lavage neutrophils and interleukin-8 levels, goblet cell hyperplasia, and basement membrane thickening.⁷

Studies also suggest that marijuana smokers have respiratory health effects similar to those of tobacco smokers. An analysis of the National Health and Nutrition Examination Survey data in 6,728 adults found that individuals who smoked marijuana at least 1 once per day within the previous month had an increased risk of persistent respiratory symptoms, such as cough, phlegm, and wheezing, with odds ratios very similar to those calculated for tobacco smokers.⁸ Such is the case with our patient, M.P.D., described in the vignette, who has a history of chronic phlegm production. Unlike tobacco, smoking marijuana was not associated with greater odds of shortness of breath or pneumonia, or objective measures, such as the physician's respiratory findings and FEV₁.⁹ In addition, Hancox et al¹⁰ demonstrated, in a cohort of 1,037 frequent (at least weekly) marijuana smokers, that smoking cessation results in significant decreases in morning cough, sputum production, and wheeze, down to similar levels as nonusers.

Robinson et al measured pre- and post-bronchodilator spirometry and impulse oscillometry (IOS) in a cohort of 915 individuals with and without asthma and found a significant association between marijuana joints-years smoked, increased peripheral airways resistance (R5–R20), and lung hyperinflation without change in FEV₁. In contrast, long-term tobacco use was associated with lower FEV₁ but not with higher peripheral resistance measurements.¹¹

These studies demonstrate persistent respiratory symptoms associated with both tobacco and marijuana smoking, although the primary disease location may differ (tobacco: central airways; marijuana: peripheral airways). Smoking marijuana increases bronchodilation via the cannabinoid receptor 1 on bronchial smooth muscle cells, likely by inhibition of cholinergic contraction.¹² This bronchodilator effect may facilitate deeper lung penetration for the tar components in marijuana smoke compared with tobacco smoke. Differences in smoking maneuvers, such as deep inspiration and Valsalva maneuvers used to maximize systemic absorption, may also contribute to greater penetration into the small airways with marijuana smoking. As such, clinicians should be aware that the chest exam and FEV₁ measurements in patients with asthma who smoke marijuana may not be sensitive indicators of risk, as much of the disease is concentrated in the peripheral airways. Physicians should consider supplementing regular lung function with IOS measurements to assess the degree of airway disease in these patients. Because there is some evidence that marijuana smokers develop

precipitins to fungal elements that contaminate the plant, the potential for small airway diseases other than asthma, such as hypersensitivity pneumonitis, should be considered in smokers with focal small airway dysfunction on IOS.¹³

Immunoglobulin E–Mediated Effects of Marijuana

Besides the nonspecific health effects of tar components, marijuana smoke also contains allergenic components. As such, clinicians should consider specific immunoglobulin E (IgE)–mediated effects in atopic patients who smoke marijuana and present with persistent respiratory symptoms. These reactions predominantly occur when *Cannabis* is consumed by smoking or vaporizing but can also arise from passive second-hand exposure to *Cannabis* smoke, indirect cutaneous transmission, or inhalation of *Cannabis sativa* pollen.^{14,15}

The primary allergenic component in marijuana is thought to be Can s3, a nonspecific lipid transfer protein.¹⁶ Because nonspecific lipid transfer proteins are ubiquitously present throughout the plant and animal kingdoms, including fruits and vegetables, cross-reactivity to Can s3 likely explains the unusually high variety of allergies to fruits, vegetables, and nuts that has been described as the *Cannabis*-plant food syndrome. *Cannabis*-sensitive patients frequently demonstrate allergies to foods (banana, tomato, citrus, and grapefruit) not associated with the typical Bet v1 oral allergen syndrome, and the severity of reactions in *Cannabis*-plant food syndrome is greater than with classical oral allergen syndrome, perhaps because Can s3 is resistant to gastric acid proteolysis. Interestingly, allergic reactions to these plant foods are often triggered or exacerbated by cofactors such as exercise or nonsteroidal anti-inflammatory drugs, similar to what has been described for food-dependent exercise-induced anaphylaxis.¹⁷ As such, clinicians should consider marijuana sensitization not only in patients with asthma or allergic reactions after exposure or ingestion, but also in patients with a history of new allergic reactions related to multiple foods.

Measuring Exposure and Sensitization

A thorough history of marijuana exposure and its relationship to allergic and respiratory symptoms should be elicited at every clinic visit. If possible, use of a validated questionnaire, such as the 21-item Marijuana Smoking History Questionnaire is preferred.¹⁸ Objective screening can be performed for the metabolite of *Cannabis*, 11-nor- Δ^9 -THC-carboxylic acid, in urine by enzyme-linked immunosorbent assay, with confirmation by gas chromatography–mass spectrometry.⁴ Unfortunately, there is currently no validated questionnaire for reporting passive exposure to marijuana and clinicians should interpret a negative questionnaire with caution as children living with parents who deny tobacco usage are often found to have objective measures of exposure. Objective measurements are therefore clearly needed to measure exposure, although the sensitivity for detecting passive exposure by measuring urinary 11-nor- Δ^9 -THC-carboxylic acid is presently unknown. Because gas chromatography–mass spectrometry measurements are more sensitive and specific than enzyme-linked immunosorbent assays, this measurement should be considered as a first-line approach to assess for passive exposure if suspicion for passive exposure is high and families deny usage.

Sensitization to *Cannabis* can be documented by prick-to-prick or “puddle” using a broad variety of raw materials such as macerated *C sativa* leaves, buds, and flower. As with any prick-to-prick approaches, this method is nonstandardized, potentially resulting in false-negative (if protein content is inadequate) or false-positive (due to irritant reactions) results. Serum specific IgE antibodies to industrial hemp can also be obtained from Thermo Fisher Scien-

tific (Uppsala, Sweden), but this assay has not yet been clinically validated.

Further Thoughts on the Clinical Vignette

In addition to the long-term effects of marijuana use secondary to the irritating and inflammatory effects of the metabolites on the airway, smoking marijuana also carries with it an acute, even life-threatening risk of barotrauma and bullous lung disease, from maneuvers users practice. These maneuvers include successive deep inhalations followed by a prolonged Valsalva maneuver or a Muller maneuver through a high resistance apparatus or against a closed glottis. These maneuvers can create marked negative intrathoracic pressure and transmural pressure gradient, which can induce the air leak. Our case described earlier exemplifies this with a complication of pneumo-mediastinum, but pneumothorax and epidural pneumatosis have also been reported.¹⁹ Of note, M.P.D. did not present with significant respiratory distress or crepitus, but a high index of suspicion raised the issue an association between the finding of an air leak and marijuana use.

Conclusion

Although the potential benefits of *Cannabis* are being researched in many disease conditions, our perspective is that there may also be public health hazards that need to be considered from both active and passive exposure to *Cannabis*. Given the increased prevalence of marijuana exposure, it is important that allergists and clinical immunologists include exposure to recreational drugs in their evaluation of unusual presentations of allergic disease. Although investigations into effects of *Cannabis* on asthma have begun, more work is needed on its effects in other respiratory diseases, upper airway conditions, and allergic skin diseases. It is important to note that *Cannabis* is composed of many cannabinoids. THC is known as the major constituent, which can induce alterations in cognitive dysfunction and behavior, but other components of *Cannabis*, such as cannabidiol, may have potential beneficial medical uses.²⁰ Due to lot-to-lot variation in different preparations of *Cannabis*, its effects may be unpredictable and objective testing is required to determine which component(s) of *Cannabis* are inducing the clinical effect under evaluation. The mind-altering effects of *Cannabis* may also affect medication adherence and perception of illness severity. As such, we are only in the early stages of our understanding of the potential harmful and beneficial effects of widespread use of *Cannabis*.

References

- [1] Retail Marijuana Public Health Advisory Committee. Monitoring Health Concerns Related to Marijuana in Colorado: 2016. Executive Summary. <https://www.colorado.gov/pacific/cdphe/marijuana-health-report>. Accessed January 3, 2018.
- [2] National Survey on Drug Use and Health (NSDUH 2016). <https://www.datafiles.samhsa.gov/study/national-survey-drug-use-and-health-nsduh-2016-nd17184>. Accessed January 3, 2018.
- [3] Wang GS, Le Lait MC, Deakyn SJ, Bronstein AC, Bajaj L, Roosevelt G. Unintentional pediatric exposures to marijuana in Colorado, 2009–2015. *JAMA Pediatr*. 2016;170:e160971.
- [4] Berthet A, De Cesare M, Favrat B, et al. A systematic review of passive exposure to *Cannabis*. *Forensic Sci Int*. 2016;269:97–112.
- [5] Young-Wolff KC, Tucker LY, Alexeeff S, et al. Trends in self-reported and biochemically tested marijuana use among pregnant females in California from 2009–2016. *JAMA*. 2017;318:2490–2491.
- [6] Gates P, Jaffe A, Copeland J. *Cannabis* smoking and respiratory health: consideration of the literature. *Respirology*. 2014;19:655–662.
- [7] Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP. Airway inflammation in young marijuana and tobacco smokers. *Am J Respir Crit Care Med*. 1998;157:928–937.
- [8] Moore BA, Augustson EM, Moser RP, Budney AJ. Respiratory effects of marijuana and tobacco use in a U.S. sample. *J Gen Intern Med*. 2005;20:33–37.

- [9] Kempker JA, Honig EG, Martin GS. The effects of marijuana exposure on expiratory airflow. A study of adults who participated in the U.S. National Health and Nutrition Examination Study. *Ann Am Thorac Soc*. 2015;12:135–141.
- [10] Hancox RJ, Shin HH, Gray AR, Poulton R, Sears MR. Effects of quitting *Cannabis* on respiratory symptoms. *Eur Respir J*. 2015;46:1–4.
- [11] Robinson PD, King GG, Sears MR, Hong CY, Hancox RJ. Determinants of peripheral airway function in adults with and without asthma. *Respirology*. 2017;22:1110–1117.
- [12] Grassin-Delyle S, Naline E, Buenestado A, et al. Cannabinoids inhibit cholinergic contraction in human airways through prejunctional CB1 receptors. *Br J Pharmacol*. 2014;171:2767–2777.
- [13] Kagen SL, Kurup VP, Sohnle PG, Fink JN. Marijuana smoking and fungal sensitization. *J Allergy Clin Immunol*. 1983;71:389–393.
- [14] Decuyper II, Faber MA, Sabato V, et al. Where there's smoke, there's fire: Cannabis allergy through passive exposure. *J Allergy Clin Immunol Pract*. 2017;5:864–865.
- [15] Silvers WS, Bernard T. Spectrum and prevalence of reactions to marijuana in a Colorado allergy practice. *Ann Allergy Asthma Immunol*. 2017;119:570–571.
- [16] Larramendi CH, López-Matas MÁ, Ferrer A, et al. Prevalence of sensitization to *Cannabis sativa*. Lipid-transfer and thaumatin-like proteins are relevant allergens. *Int Arch Allergy Immunol*. 2013;162:115–122.
- [17] Decuyper II, Van Gasse AL, Cop N, et al. *Cannabis sativa* allergy: looking through the fog. *Allergy*. 2017;72:201–206.
- [18] Cuttler C, Spradlin A. Measuring *Cannabis* consumption: psychometric properties of the Daily Sessions, Frequency, Age of Onset, and Quantity of *Cannabis* Use Inventory (DFAQ-CU). *PLoS ONE*. 2017;12:e017819.
- [19] Hazouard E, Koninck JC, Attucci S, Fauchier-Rolland F, Brunereau L, Diot P. Pneumothorax and pneumomediastinum caused by repeated Müller's maneuvers: complications of marijuana smoking. *Ann Emerg Med*. 2001;38:694–697.
- [20] Mouness JS, Siegel JA, Dunnick CA, Dellavalle RP. The role of cannabinoids in dermatology. *J Am Acad Dermatol*. 2017;77:e87–e88.