Clinical Commentary Review

Occupational Allergies to Cannabis

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Learning objectives:

1. To appreciate the nuances of cannabis industry operations in the 21st century and identify the potential biological and chemical hazards in the occupational environment.

2. To understand the spectrum of symptoms associated with cannabis allergy.

3. To formulate a strategy for diagnosis and management of symptomatic cannabis workers.

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Within the last decade there has been a significant expansion in access to cannabis for medicinal and adult nonmedical use in the United States and abroad. This has resulted in a rapidly growing and diverse workforce that is involved with the growth, cultivation, handling, and dispensing of the cannabis plant and its products. The objective of this review was to educate physicians on the complexities associated with the health effects of cannabis exposure, the nature of these exposures, and the

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Abbreviations used
SPT- skin prick test
THC- Δ^9-tetrahydrocannabinol

future practical challenges of managing these in the context of allergic disease. We will detail the biological hazards related to typical modern cannabis industry operations that may potentially drive allergic sensitization in workers. We will highlight the limitations that have hindered the development of objective diagnostic measures that are essential in separating "true" cannabis allergies from nonspecific reactions/irritations that "mimic" allergy-like symptoms. Finally, we will discuss recent advances in the basic and translational scientific research that will aid the development of diagnostic tools and therapeutic standards to serve optimal management of cannabis allergies across the occupational spectrum. **(J Allergy Clin Immunol Pract 2020;8:3331-8)**

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INTRODUCTION

Cannabis has a complex and controversial interaction with human society, albeit an enduring one. Historically, industrial hemp, the cannabis plant that contains less than 0.3% Δ^9-tetrahydrocannabinol (THC) (soft hemp), has been an essential component in industries as an important source of fiber, paper, cordage, food, and medicine.[1] However, cannabis cultivation (containing more than 0.3% THC) and access to its products are largely restricted throughout the world because of its secondary properties of psychoactive compounds. In the United States, cannabis and its components (particularly cannabinoids) are designated by the federal Drug Enforcement Administration as Schedule I controlled substances, whereas in Canada and several European countries they have either been legalized or decriminalized for medicinal or adult nonmedical use. In the past few decades, cannabis has gained popularity primarily for its medicinal properties in managing symptoms of chronic illnesses including for pain management, posttraumatic stress disorder, and certain seizure disorders.[2-4] Furthermore, along with its psychotropic effects, it is a source of plant protein food and continues to be used in textile industries.[5,6]

Worldwide, cannabis is the most frequently used illicit drug.[7] The United Nations Office on Drugs and Crime survey recently reported that approximately 10% of the US population (and up to 5% of the world population) uses cannabis in some form for medicinal or adult nonmedical purposes.[7] Increased legalization and expanding access to cannabis within the United States and elsewhere has also ushered in new economic and employment opportunities for this growing industry. Currently, more than 240,000 workers are estimated to be engaged in various cannabis-related business operations (eg, cultivation, processing, and dispensaries) across the United States, and these numbers will likely increase in the near future.[8] This brings into focus a concern for the health and well-being of workers who will be exposed to the plant and its byproducts, specifically potential allergic reactions to cannabis. Although there is some evidence on allergic sensitization to cannabis, these are limited and consist mostly of case reports; consequently, it is not possible to definitively establish the true burden of cannabis allergy, especially within occupational environments. In this review, our goals are to provide a brief background into the biological hazards associated with job activities in the cannabis industry, identify the risk factors that may contribute toward the development of cannabis-related allergic reactions, and provide insight into the current practice of diagnostics and therapeutics for the clinical management of occupational allergies to cannabis.

HEMP DUST AND BYSSINOSIS

Cannabis has been heavy used in the textile industry for the production of fiber-based raw material called hemp, which is produced from various cannabis plants and contains less than 0.3% THC. Most of our understanding of occupational exposures within cannabis industries comes from a series of studies published on cultivation and processing of soft hemp.[9-19] Collectively, these studies have shown that the pathophysiology of cannabis exposures in the workplace is complicated by the presence of other occupational hazards such as bacteria (endotoxins) and other nonspecific irritants that result in dust-related disease called "byssinosis." Furthermore, endotoxin from bacteria present on plant may continue to persist in processed fibers and contribute to byssinosis,[12] although more studies are needed. Byssinosis is a lung disease characterized by airflow obstruction and airway inflammation caused by airborne organic dust in the occupational environment.[20] It was first described in hemp workers and termed "cannabosis,"[10] and was a particular concern in workers who directly handled (batting and hackling) retted soft hemp.[12] Although byssinosis is commonly associated with other organic fibers such as cotton,[21] flax,[22] and jute,[23] hemp workers are most highly affected, with prevalence rates of up to 44% in some studies.[11,12] Byssinosis, regardless of the specific fiber involved, typically develops following sustained exposures for more than 10 years. It is characterized by symptoms of severe bronchial hyperresponsiveness on the first day of the work week, with declining symptoms on consecutive days of exposure.[19] Symptoms will flare on reexposure following several days away from work such as weekends or holidays. Byssinosis, however, is not mediated by specific IgE antibodies and is not explained by allergic sensitization to cannabis. We speculate that modern-day cultivation and manipulation practices of cannabis may be less likely to generate organic dust at the rates previously observed with hemp cultivation, although more studies are needed.

MODERN-DAY CANNABIS OPERATIONS AND ASSOCIATED EXPOSURE RISKS

Cannabis industries in the 21st century

Within the last decade, numerous states have passed laws that have either expanded access to cannabis or decriminalized it for medicinal and/or adult nonmedical use. The Hemp Farming Act of 2018 rescheduled hemp to a legal agricultural commodity, whereas strains of cannabis with more than 0.03% THC continue to be identified as Schedule I controlled substance. This shift in approach and regulation has resulted in the emergence of businesses to cultivate cannabis, manufacture related products, and set up distribution/sales networks (including dispensaries). In 2018, the cannabis industry was valued at more than $11 billion, and recent estimates have projected an annual growth rate of 14.5% per year through 2025.[24] The rapid growth of the

cannabis industry in the United States has resulted in the employment of a workforce that has approached nearly 250,000 workers.[25] However, because cannabis-related operations are highly varied, there are emerging health concerns for workers within the industry. The growth of the cannabis industry has focused the attention of employee unions, state public health agencies such as the Colorado Department of Public Health and Environment, and federal government agencies such as the National Institute for Occupational Safety and Health on workplace safety and health hazards.[26,27] In states such as Colorado, where medicinal and adult nonmedical use of cannabis is legal, specific guidelines have been established to ensure worker safety in this evolving economic endeavor.[26] Although these recommendations are broad, they are intended to assist in identifying specific hazards present in the industry and are somewhat tailored to the practices within the cannabis industry.

Although cannabis cultivation and harvesting operations are analogous to any other plant-based agricultural and manufacturing practices, recent investigations have revealed unique occupational safety and health considerations that need to be considered.[27] In a recent study conducted by the researchers at the Colorado School of Public Health, potential respiratory hazards and health effects were among the most frequently reported concerns by cannabis cultivation workers.[28]

Figure 1 illustrates the occupational workflow within a contemporary cannabis grow facility, as well as the associated exposure risks, although specific practices may vary owing to the dynamic nature of the industry. Throughout the growth cycle of the cannabis plant, a number of tasks involve direct handling of the plant. Although these tasks vary in duration, they carry a significant risk of allergic sensitization. Secondary exposure to other allergens (such as fungi), bacteria, endotoxin, pesticides, cannabinoids, and volatile compounds also poses health risks.

Other occupational settings for Cannabis exposure

Additional occupations that are at risk of cannabis exposure include law enforcement personnel, laboratory technicians, and dispensary workers. Evidence of the adverse health effects of occupational exposure to cannabis (including allergies) emerges from studies evaluating law enforcement personnel with direct contact with illicitly grown cannabis,[30,31] or from second-hand exposure at work.[32] Law enforcement workers may also be exposed to pesticides and high concentrations of microbial bioaerosols when removing illicit cannabis plantations or "indoor grow" operations.[30,31]

In summary, many of those occupationally exposed to cannabis, whether it is on farms cultivating cannabis, downstream cannabis processing industries, or during forensic work, have the potential to experience respiratory and dermal allergic symptoms that could be potentially anaphylactic. Various biological and chemical hazards can contribute to this symptomology, as well as host specific factors.

OCCUPATIONAL CANNABIS ALLERGIES AND SYMPTOMS

Studies describing the health effects of working in a cannabis-rich environment have been limited. Nevertheless, some studies have demonstrated that direct handling of plant material can contribute to allergic sensitization in workers with infrequent exposures such as law enforcement officers and forensic technicians.[33-37] Immediate respiratory symptoms in direct response to

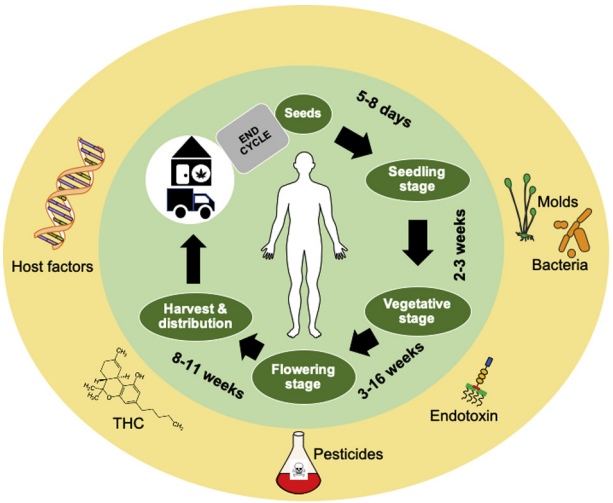

FIGURE 1. Primary and secondary health hazards associated with occupational exposures to cannabis. An investigation into a simplified flow of the occupational tasks that occur within the cannabis industry indicates numerous opportunities for direct (and possibly prolonged) exposures to cannabis that may affect worker health and drive allergic sensitization. The green sphere describes the cycle of cannabis cultivation, processing, and distribution and emphasizes the risk of direct exposures to the plant. Workers involved in cultivation, destemming, and trimming operations may have elevated risks for disease owing to prolonged direct contact with the plant. Exposure to cannabis-related biological hazards is not limited to just the grow facility, and could extend to transportation workers, budtenders, or retailers. The yellow sphere identifies potential secondary risk factors that may drive sensitization alone (mold) or act as adjuvants (endotoxin, pesticides, THC) and promote cannabis sensitization. Furthermore, underlying host factors such as atopy and asthma may represent risks for exacerbation and diseases. Indoor work environments, if poorly ventilated, may also increase sensitization risk. Cannabis grow cycle details obtained from www.leafly.com.[29]

exposure are more common and are marked by nasal congestion, rhinoconjunctivitis, and/or chest symptoms such as cough, wheeze, chest tightness, or shortness of breath related to bronchial hyperresponsiveness.[33-36,38] These are in contrast to the delayed respiratory symptoms of byssinosis in hemp workers, with temporal decrease in severity over the course of the work week. Furthermore, cutaneous symptoms such as (contact) urticaria, angioedema[34,35,37,38] and rarely, delayed dermatitis-like[33] symptoms have been reported following direct contact with the cannabis plant. These are similar to those observed in adult nonmedical users with cannabis allergy, demonstrating varying degrees of respiratory, cutaneous, gastrointestinal, and cardiovascular symptoms.[39-43] Up to 20% of affected individuals may also show anaphylactic-like reactions.[39] Also, rarely occurring, anaphylactic reactions have been reported in sensitized individuals associated with hempseed ingestion, which is marketed as a "healthy protein food."[44] One peculiar feature of cannabis allergy in European adult nonmedical users is the high prevalence of IgE-mediated cross-reactivity syndrome with multiple plant foods (such as peach and tomatoes).[42,45-47] Interestingly, the severe cross-reactivity with other plant allergens is not common

TABLE I. Laboratory-based approaches for molecular diagnosis of cannabis allergies

Diagnostic approach	% Sensitivity (analyte)	% Specificity (analyte)	Relevant references
ImmunoCAP (hemp)	86% (hemp extract)	32% (hemp extract)	[39,56]
Basophil activation test	63% (crude cannabis extract) 71% (recombinant Can s 3)	67% (crude cannabis extract) 85% (recombinant Can s 3)	[39]
Cytometric bead array	63% (recombinant Can s 3)	87% (recombinant Can s 3)	[39]
Immunoproteomics	Not applicable	Not applicable	For additional details[40]

Currently, a specific IgE test for cannabis (hemp) is available for research use only. Can s 3 represents nonspecific lipid transfer protein, which is a major allergen of cannabis.

in occupational cannabis allergy,[48] although detailed studies are lacking. It is possible that different routes of exposure, inhaled and ingested versus primarily cutaneous contact, result in different patterns of allergic reactivity. A recent study of the Belgian police force could not objectively establish a cannabis allergy as the cause of the respiratory and/or cutaneous symptoms reported by 42% (34 of 81) of symptomatic participants during occupational cannabis exposure.[45]

Relevance of cannabis pollen to occupational exposures

Cannabis grow operations may also involve exposure to cannabis plant pollen. Similar to Birch trees, which are highly allergenic,[49] cannabis produces large quantities of anemophilous pollen. Pollen exposure of cannabis-sensitized patients, established by skin prick test (SPT) to cannabis pollen, has been shown to cause allergic symptoms such as rhinoconjunctivitis.[36,50-52] However, modern-day cannabis cultivation practices have taken advantage of the dioecious nature of the plant. Specifically, practices involve seeding of the plant and early removal of male plants (that bear pollen) during growth to specifically enrich female plants to develop seedless buds (in absence of pollination) that are rich in cannabinoids.[53] Other operations bypass pollination concerns through seedless propagation of only female clones. Thus, depending on the nature of the grow facility, pollen from male plants may not, or minimally, be of concern for occupational exposures. However, breeders who are developing new genetic strains could be periodically exposed to pollen from male plants.

Cannabis allergens

Most biological allergens are typically classified as high molecular weight—proteinaceous compounds such as *Hevea* latex, pollens, enzymes, and cereals.[54] Investigations of adult nonmedical cannabis allergies have found that type I hypersensitivity mechanisms involving allergen-specific IgE antibodies are predominant.[39,40,43,55] A growing number of studies have identified putative allergens from cannabis (Table I), with nonspecific lipid transfer protein (Can s 3) as a major allergen and oxygen-evolving enhancing protein 2 (*Can s 4*) as a relatively minor allergen.[40,42,43,48,57,58] Can s 3, the major cannabis allergen, has been proposed as the driver of plant-food cross-reactivities observed in cannabis allergy in Europe (but not in the United States).[39,42] This is primarily due to the high degree of similarities between the different nonspecific lipid transfer proteins in the plant kingdom and a sequence of conserved amino acid sequences in the C-terminal region of the mature protein.[55,59] It is important to emphasize that these cannabis allergens were primarily identified, and subsequently validated, in adult nonmedical users. In contrast, sensitization to nonspecific lipid transfer protein did not appear to be responsible for symptoms from cannabis exposures in law enforcement officers.[45] Identification and validation of additional cannabis allergens relevant to occupational exposures is needed.

In addition, the cannabis plant contains a large number of low-molecular-weight components including cannabinoids, terpenes, and volatile organic compounds, which can exert immunomodulatory actions. Indeed, the first report describing cannabis allergies speculated a role for THC.[60] However, these low-molecular-weight cannabis chemicals have not been reported to act as allergens. Some studies have also suggested that carbohydrate moieties (including cross-reactive carbohydrates) on cannabis proteins could bind to serum IgE.[40,61] However, a mechanistic role for polysaccharides acting as cannabis allergens has not been investigated.

DIAGNOSIS OF CANNABIS ALLERGY

Currently, there are no diagnostic tests available to diagnose true cannabis allergies. In this section, we will provide an overview of the lessons learned from clinical management of suspected cannabis allergy cases. Furthermore, we will discuss the research findings that have furthered our understanding of the underlying type I hypersensitivity mechanisms, although they have been applied in laboratory settings only.

Clinical diagnostics

a. Patient exposure history, symptoms, and physical examination. The first step in diagnosing occupational cannabis allergy is to clearly establish the nature of a patient's job within the cannabis industry and a thorough evaluation of their exposure history. An emphasis should be placed on the timing of symptoms subsequent to exposure, with some period of latency before symptoms onset. Questions should be included regarding the history of exposure (eg, duration of time in the job, type of exposure, and working conditions), personal use (eg, frequency and duration of use, routes of administration, and adverse events), presence of plants grown within the home, as well as potential secondary exposures.

IgE-mediated allergies typically present with symptoms within minutes to 2 to 4 hours following exposure. They typically resolve promptly following cessation of exposures, although they may also induce nonspecific bronchial hyperreactivity and/or a late-phase response as classically was found with bakers.[62] The pattern of symptoms is essential to rule out byssinosis, which is non−IgE-mediated. The spectrum of cannabis symptoms often includes allergic rhinitis and new onset or exacerbation of underlying asthma. Furthermore, cutaneous manifestations such as contact urticaria may be present in workers who directly handle or come into contact with the plant.[33] However, the potential for effects from nonspecific irritants cannot be ruled out. Finally,

TABLE II. List of cannabis allergens and allergen-candidates

Cannabis allergen	WHO/IUIS allergen nomenclature	References
Nonspecific lipid transfer protein	Can s 3	42,43,46,48,58
Oxygen-evolving enhancing protein 2	Can s 4	40,57
Ribulose-1,5-bisphospate carboxylase/oxygenase	Not validated	40
Thaumatin-like protein	Not validated	46

WHO/IUIS, World Health Organization/International Union of Immunological Societies.
All allergens identified here have emerged from investigations into allergic sensitization to cannabis among adult nonmedical users. Can s 3 and Can s 4 allergens have been assigned as major and minor allergens, respectively. All allergens reported here have not been validated under occupational exposure settings.

atopy may be a risk factor for other IgE-mediated allergies such as cannabis; hence, establishing a patient's history of atopy or asthma is also valuable.

As with other inhalant allergies, signs include allergic rhinoconjunctivitis, urticaria, and dermatographism, along with wheeze, cough, or a prolonged expiratory phase.[38,41,56,57,63] Although a specific bronchial challenge (SBC) is considered the criterion standard to diagnose cannabis-induced asthma, it is difficult to perform because of legal and ethical concerns.

b. Skin prick testing. This is one of the most easily accessible diagnostic methods in a clinical office and can be performed with either purified extracts or fresh material. In occupational settings, samples can be collected from operational sites.[13,64] Tasks that involve direct handling of plant material may contribute to a higher prevalence of SPT positivity.[13,64]

c. Inhalation challenge. Although an SBC is considered the criterion standard to diagnose cannabis-induced asthma, it is difficult to perform because of legal and ethical concerns. As in other cases of occupational and nonoccupational asthma, a methacholine challenge may be performed, if needed, to confirm an asthma diagnosis.

d. Laboratory-based approaches for molecular diagnosis of cannabis allergies. In an effort to develop standardized tests to diagnose cannabis sensitization, multiple researchers have sought to identify specific molecular mediators of sensitization (summarized in Table I). As a result, a number of allergens relevant to adult cannabis use allergy have been identified and some validated (Table II). However, none of these tests are available clinically.

In summary, it is essential that the workplace conditions are taken into consideration when examining symptoms related to occupational cannabis exposure. The methods described herein to establish sensitization to cannabis allergens in occupational settings will require substantial validation for clinical use. Because cannabis is often not the only allergen present in the grow operation or dispensary, symptoms can be elicited by other inhalant allergens (eg, fungi).[41] Efforts into identification and validation of relevant allergens and their integration into SPT-based in-clinic assessments can substantially improve the ability to establish true cannabis allergies in the clinic itself. On the basis of diagnostic algorithm developed by our colleagues in Belgium for establishing cannabis allergy in adult nonmedical users,[58] we propose modifications that may be suitable for assessing occupational cannabis allergies (Figure 2).

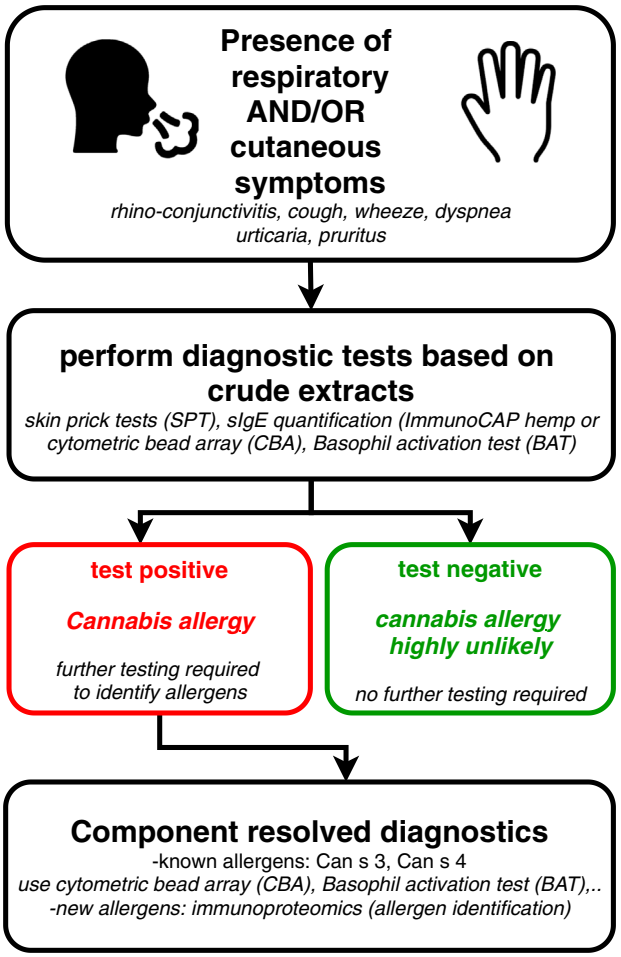

FIGURE 2. Flowchart showing proposed diagnostic steps in establishing occupational cannabis allergies. This scheme is based on evidence from examining allergic sensitization to cannabis among nonmedicinal users. In absence of strong evidence from occupational allergy cases, this diagnostic algorithm should be considered as a proposal with an expectation that this approach will be refined as more data are available in the future. As indicated, literature indicates that testing should be done only in symptomatic individuals. Any symptomatic exposure to cannabis in the workplace will need thorough evaluation of the exposure history. Although asymptomatic workers are unlikely to seek medical attention, this group may be included in any employment prescreening, surveillance, and monitoring programs. SPT with crude protein extracts generated from cannabis or from dust samples from specific operations may be helpful in establishing specific allergic sensitization. Furthermore, additional laboratory-based investigations using ImmunoCAP, BAT, CBA (with specific allergens Can s 3 and Can s 4), and immunoproteomics will assist in allergen identification and validation. In workers with a negative SPT result to crude allergens, further testing is not essential. For negative SPT result to specific allergens, cannabis allergies could still be possible, although it rules out Can s 3 and Can s 4 as potential allergens. *sIgE*, Specific IgE.

Challenges associated with developing diagnostics

Although significant strides have been made in understanding the profile of true cannabis allergies, many challenges exist.[65] Although cannabis is popularly understood as a single entity, there are more than 10,000 varieties and the list is constantly growing with the introduction of new strains. Accounting for differences within strains is currently not feasible for each study. The current legal status of the plant, and the practical challenges of studying Schedule I substances in the United States, have also contributed to the challenges. More recent studies indicate that cannabis exposure by itself is not always sufficient to explain symptomatic outcomes.[45] Cannabis grow facilities are heterogeneous operations where workers are exposed to many other possible triggers that are associated with the plant, soil, or components of the surrounding environment. Indeed, secondary sources of exposure including bacteria, fungi, and endotoxin have recently been identified in several National Institute for Occupational Safety and Health health hazard evaluation studies.[66-70] Overall, the endotoxin levels measured were substantially lower than those reported in earlier studies of the European hemp industry and were lower than the Dutch Expert Committee on Occupational Safety exposure limit of 90 EU/m^3.[17,71] 16S gene sequencing of worker's breathing zone samples also identified a broad diversity of bacterial species including Actinobacteria.[66,69] Fungi are also common contaminants due to the requirement of high humidity conditions for cannabis plant growth, particularly during the seedling stage, and have been found in administrative areas and personal samples in the National Institute for Occupational Safety and Health's health hazard evaluations.[66,67,69] Pathogens such as *Botrytis cinerea* that causes gray mold disease on the cannabis plant have been reported, including in personal worker breathing zone samples.[69]

TREATMENT OF CANNABIS ALLERGIES

Typically, complete avoidance of the offending sources of allergen can lead to symptomatic improvement. This can be challenging in an occupational setting but may be necessary in the case of anaphylaxis. Use of personal protective equipment and introduction of engineering and administrative mitigation efforts may also minimize or eliminate the risk for workers.

Antihistamines, topical nasal steroids, bronchodilators, and inhalers may be helpful to manage symptoms. In general, immunotherapy has not been used extensively for treating occupational allergies.[72,73] There is only 1 case report (conference proceeding) describing successful immunotherapy for occupational cannabis allergy symptoms (including anaphylaxis) with the help of omalizumab.[74] In the future, designed protocols with exposure to smaller amounts of crude cannabis proteins may assist in establishing immunotolerance.

CONCLUDING REMARKS

With legalization of cannabis, there has been a gradual emergence of workers presenting with allergic symptoms from employment in the cannabis industry, handling cannabis during law enforcement activities, as well as adult nonmedical users.[34,41,45] Less stigmatization, and a greater openness to discuss with health care providers, may also play a role in increased documentation and awareness. There may be reservations about handling a federally illegal, even if state-sanctioned, cannabis product; however, the priority of caring for the patient's health may outweigh this dilemma, because getting clarity on what can be achieved clinically may be needed. Although the history and clinical presentation of symptoms can help in differentiating allergic from nonallergic cases, specific diagnostic measures may be critical to further help this distinction. The most accessible technique remains SPT, which can be performed with fresh materials, preferentially originating from the patient's environment, or with laboratory-produced standardized extracts. However, these techniques remain highly variable and the sensitivity may vary. Laboratory-based approaches may provide more insight into identifying the molecular drivers of cannabis allergy; however, these are currently for research use only. Symptoms may also be caused by irritant exposures leading to reactive airways dysfunction syndrome, complicated by the presence of plant cannabinoids that have immunomodulatory properties. There is some evidence as well for delayed-type hypersensitivity reaction demonstrated by positive patch testing[35] in a forensic worker, and in early *in vitro* experiments.[75] Eventually, the development of objective diagnostic measures will be helpful in separating true IgE-mediated cannabis allergies from nonimmunologic irritant reactions to the plant and the industry.

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