25(OH)D levels. Vitamin D supplementation did not affect the ACT score or forced expiratory volume in 1 second (Fig 1B and C). However, because the patients' conditions were relatively well controlled at entry, this could have influenced the results.

When data were pooled using all serum 25(OH)D levels matched to the ACT scores for each of the 3 time points measured, a significant positive correlation was found (Pearson $r = 0.25$, $P < .05$). An inverse correlation of serum 25(OH)D and BMI was found (Pearson $r = 0.3$, $P < .05$).

There are important considerations from our data regarding the relationship of vitamin D and asthma. First, significant seasonal variation in 25(OH)D levels occurred, emphasizing the importance of obtaining multiple 25(OH)D levels throughout a study to allow for increases in 25(OH)D levels due to sun exposure. Even though those in the placebo group had an increase in serum 25(OH)D level in the summer, most individuals were still vitamin D insufficient (58.3%).

Second, to assess the therapeutic effect in asthma, a significantly higher dose of vitamin D supplementation will be necessary beyond the recommendation of the Institute of Medicine (600 IU)[6] or the American Academy of Pediatrics (400 IU).[7] We observed in our study population that 1,000 IU was inadequate to increase 25(OH)D levels more than 30 ng/mL in 50% of our study participants after 1 year of supplementation. This is likely dependent on the individuals because factors such as diet and sun exposure contribute to a person's 25(OH)D level. Most of our study participants were black or Hispanic, and many were overweight at baseline, with a mean BMI of 24.5. Vitamin D deficiency has been linked to being overweight and having darker skin color.[8] Future studies should consider higher doses of vitamin D or, preferably, serial titration to sufficiency to ensure sufficient 25(OH)D levels.

Third, future therapeutic trials should be powered sufficiently, and patients supplemented to vitamin D levels greater than 30 ng/mL during the entire study to reveal the potential for vitamin D supplementation to improve asthma control. In this study, no significant differences were found in ACT scores or spirometry values between vitamin D–treated and placebo-treated individuals. This may have been a result of failure to achieve normal 25(OH)D levels in most vitamin D–treated patients. The study was likely underpowered with a relatively large dropout rate (33.3%). However, when the ACT data obtained from all visits were pooled, a positive correlation was found between serum 25(OH)D levels and ACT scores, suggesting an effect of vitamin D in asthma management.

Fourth, secondary end points for therapeutic benefit should be expanded, possibly adding serial methacholine challenges and nitric oxide measures, which might show interim benefit.

Because vitamin D has a number of potential important effects in asthma, this line of investigation is important. However, future studies need to be conducted for at least 1 year with higher levels of vitamin D supplementation and a larger number of individuals to truly determine the significance of vitamin D in asthma.

Elena Lewis, MD
Cristina Fernandez, MD
Aikaterini Nella, MD
Russell Hopp, DO
J. Christopher Gallagher, MD and
Thomas B. Casale, MD
*Creighton University Medical Center
Omaha, Nebraska
E-mail: thomascasale@creighton.edu

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Hypersensitivity reactions to marijuana

Allergy to marijuana is generally considered to be rare. *Cannabis sativa* is an annual plant in the Cannabaceae family that pollinates during the summer months. Various parts of this plant are used for both commercial and recreational purposes. Psychoactive cannabinoid compounds, mainly Δ9-tetrahydrocannabinol (THC), are present in the flowers and, to a lesser extent, in the leaves, stems, and seeds of the plant. When derived as dried preparations of the plant parts (marijuana), the cannabinoids are consumed by smoking, vaporizing, and oral ingestion. Teas and ointments are also common preparations.

The first report of allergic reaction to *C sativa* was in 1971, when a 29-year-old woman, after smoking a marijuana cigarette for the first time, had symptoms consistent with an anaphylactic response.[1] Hypersensitivity was confirmed via skin prick testing (SPT) and passive transfer studies, suggesting an immunologic response to the THC component of the marijuana plant.[1] Since then, several case reports have been published describing allergic reactions to *C sativa* after exposures through inhalation, ingestion, or skin contact.[2–4] Reactions, including rhinoconjunctivitis, urticaria, and angioedema, have been reported.

In addition to THC, sensitization to marijuana may involve IgE directed to proteins from *C sativa*.[3] One case involved a 28-year-old man who had urticaria on contact and rhinorrhea after smoking marijuana.[4] The investigators were able to isolate a 9-kDa IgE-binding protein and identified it as a lipid transfer protein (LTP). The patient's IgE to cannabis LTP cross-reacted with the LTP from peach.[4] LTP is highly stable and cross-reacts with a large number of pollens and foods. Thus, individuals can have both type 1 hypersensitivity symptoms of rhinoconjunctivitis and anaphylactic symptoms when exposed not only by inhalation but also by ingestion

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Table 1
Skin Prick Test (SPT) results and marijuana allergy symptoms

Patient sex/age, y	SPT Results	Exposure	Symptoms	Other SPT reactivities
F/31	10-mm wheal/27-mm flare	Smoking and contact	Inhalation: conjunctivitis, rhinitis Contact: none	Amoxicillin
M/35	14-mm wheal/50-mm flare	Drinking marijuana tea, smoking, and contact	After ingestion: agitation, periorbital angioedema, anxiety, tight chest, gastrointestinal cramping, vomiting, anaphylaxis Inhalation: conjunctivitis, wheezing, tightness and abdominal cramping, periorbital angioedema Contact: urticaria, angioedema, pruritus	Peanut allergy
M/28	13-mm wheal/27-mm flare	Smoking and contact	Inhalation: rhinitis, conjunctivitis Contact: urticaria	Dust mite, cat, dog, birch, birch pollen cross-reacting foods (almond, hazelnut, peanut)
M/39	18-mm wheal/51-mm flare	Smoking and contact	Inhalation: rhinitis, conjunctivitis, periorbital angioedema Contact: urticaria	Birch, ragweed, grass, birch pollen cross-reacting foods (apple, soya, hazelnut)
M/31	13-mm wheal/29-mm flare	Smoking and contact	Inhalation: none Contact: urticaria	Dust mite, cat, dog, trees, *Alternaria*, *Cladosporium*
F/26	12-mm wheal/35-mm flare	Smoking and contact	Inhalation: rhinitis, conjunctivitis, sinusitis, periorbital angioedema, wheezing, asthmatic symptoms Contact: urticaria	Grass, dust mite, dog, components of house dust
M/31	6-mm wheal/13-mm flare	Smoking and contact	Inhalation: asthma Contact: periorbital angioedema, conjunctivitis, urticaria	Dust mite, birch
F/55	7-mm wheal/15-mm flare	Smoking and contact	Inhalation: coughing, periorbital angioedema Contact: urticaria	No known allergies
M/32	5-mm wheal/14-mm flare	Smoking, vaporizer, and contact	Inhalation: conjunctivitis, asthma Contact: periorbital angioedema	Cats, dogs, grass, *Alternaria*, *Aspergillus*
M/26	6-mm wheal/20-mm flare	Smoking and contact	Inhalation: conjunctivitis, rhinitis, asthma Contact: urticaria	Cashew, peanut, hazelnut
M/32	4-mm wheal/11-mm flare	Smoking and contact	Inhalation: conjunctivitis, eye irritation, coughing Contact: none	Latex (type 1), dust mite, birch, grass
M/26	14-mm wheal/31-mm flare	Smoking and contact	Inhalation: conjunctivitis Contact: urticaria, angioedema	No known allergies
M/41	14-mm wheal/23-mm flare	Smoking and contact	Inhalation: rhinitis Contact: urticaria	No known allergies
M/35	7-mm wheal/33-mm flare	Smoking and contact	Inhalation: periorbital angioedema, asthma, wheezing Contact: urticaria, conjunctivitis	No known allergies
M/22	9-mm wheal/21-mm flare	Smoking and contact	Inhalation: anaphylaxis Contact: urticaria	Birch, grass, ragweed, peanuts, hazelnut
M/50	19-mm wheal/50-mm flare	Smoking and contact	Inhalation: conjunctivitis Contact: urticaria	No known allergies
F/23	5-mm wheal/11-mm flare	Smoking and contact	Inhalation: none Contact: angioedema	No known allergies

and contact with *C sativa* leaves.[2] A recent study selected 140 individuals addicted to drugs or asthmatic patients with sensitization to pollen, tobacco, tomato, or latex and identified cannabis sensitization (by SPT) in 74 (53%).[5] Patients sensitized to tomato and tobacco tested positive on a cannabis bronchial challenge (52% and 61%, respectively), suggesting cross-reactivity and that these allergies may be risk factors for marijuana allergy.[5]

A cohort of 17 individuals (22–55 years of age) with symptoms of marijuana sensitivity were studied (Table 1), and ethics approval was obtained from the Canadian Shield Ethics Review Board. The immunologic basis of these responses was evaluated by SPT using an extract prepared by macerating buds and flowers in water (5 mL) for 15 minutes and stored at 4°C until use. All testing was completed within 3 months. Histamine (10 mg/mL) was used as a positive control, and human serum albumin in 50% glycerol was used as a negative control. Wheals larger than 5 mm with surrounding flare were characterized as a positive result.

Fifteen patients with inhalation exposure manifested rhinitis and conjunctivitis (9), periorbital angioedema (4), sinusitis (1), wheezing (3), and swelling of the throat sensation (1). Fifteen patients reported contact symptoms, which included 13 occurrences of urticaria and 2 of periorbital angioedema. One patient presented with anaphylactic symptoms, which included anxiety, chest tightness, wheezing, gastrointestinal cramping, and vomiting after ingestion of marijuana tea (Table 1). All of the patients reported symptoms with repeated exposures, and 15 confirmed cessation of symptoms after avoidance of marijuana.

In this study, marijuana hypersensitivity was demonstrated with a crude uncharacterized SPT reagent, and large wheal and flare responses were observed; suggesting type 1 sensitization to proteins of the cannabis plant. Five *C sativa* IgE-binding proteins have been reported, ranging from 10 to 68 kDa, using serum samples from an allergic patient, and a 9-kDa LTP has been positively identified.[4] Some marijuana allergic patients have positive SPT results to ragweed, pigweed, and tomato plants, indicating possible cross-reactivity.[2,5] Moreover, work-related contact urticaria has been reported in forensic science laboratory technicians handling marijuana. Several reports have implicated contamination with *Aspergillus* as a potential source of allergens in marijuana,[6,7] although only 1 of our patients had SPT reactivity to *Aspergillus*. Addressing marijuana allergy is difficult when assessing patient exposure history because patients may not voluntarily disclose this information even when experiencing symptoms. Future studies with standardized extracts will be needed to determine the specific allergens associated with marijuana allergy and to better understand and develop strategies for treatment.

Allergic reactions to marijuana appear to be increasing in prevalence given the increasing social use of marijuana and its expanding use for medical and ingestion purposes.[8] Because some of the

reactions are severe, it is important that clinicians address marijuana exposure when assessing a patient's exposure history.

Ayla Tessmer, BA*
Noam Berlin, BSc*
Gordon Sussman, MD†
Nathan Leader, BSc*
Eddie Chu Chung, Bsc*
Donald Beezhold, PhD‡
*Gordon Sussman Clinical Allergy Research Inc
Toronto, Ontario, Canada
†Division of Allergy and Clinical Immunology
Department of Medicine
University of Toronto
Toronto, Ontario, Canada
‡Allergy and Clinical Immunology Branch
Health Effects Laboratory Division
National Institute for Occupational Safety and Health
Morgantown, West Virginia
gsussman@rogers.com

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Anaphylaxis caused by tetrazepam without cross-reactivity with other benzodiazepines

Benzodiazepines are sedative hypnotic agents that have been in clinical use since the 1960s for sedation and to treat anxiety, seizures, withdrawal states, insomnia, and drug-associated agitation. Adverse reactions are mostly related to overdosing. Allergic reactions are rare, with only a few cases reported in the literature.

A 33-year-old man presented with systemic urticaria after the intake of 50 mg of tetrazepam. Shortly thereafter, he received treatment in the emergency department with steroids and antihistamines. Afterward, he was referred to our unit for study.

Six months after the presentation in the emergency department, skin prick testing with tetrazepam (diluted 1% water) produced a negative result. A positive control test with 100 mg/mL of histamine was performed. Then, we proceeded to a single-blind, placebo-controlled challenge oral test with 5, 5, and 15 mg of tetrazepam. The interval between doses was 30 minutes. Fifty minutes after the intake of 25 mg of tetrazepam, our patient presented with generalized pruritus, urticaria, dyspnea without wheezing, and tachycardia (heart rate, 120/min). Blood pressure and oxygen saturation were normal. We administrated treatment with adrenaline, methylprednisolone, and dexchlorpheniramine with resolution ad integrum. Blood samples for tryptase determination were taken. The basal tryptase level was 6.5 μg/L, reaching a peak of 17.5 μg/L at 90 minutes and decreasing to 4 μg/L 4 hours later. A hive appeared on the area of the forearm where the cutaneous test had been performed.

We performed prick (full strength) and intradermal tests (1/100) with midazolam, flunitrazepam, diazepam, and clorazepate, which produced negative results. Single blind placebo control challenges oral challenges with diazepam and clorazepate were performed according to the following protocol: 30 minutes between doses until a therapeutic dose of 5 mg (1, 2, and 2 mg) of diazepam and 10 mg (1, 4, and 5 mg-) of clorazepate. Both oral challenge results were negative.

Benzodiazepines are a rare cause of immediate allergic reactions, more of them in the context of general anesthesia. There are some reports of anaphylactic reactions due to endovenous diazepam[1,2] and midazolam[3], but to the date, there are no reports of such reactions induced by tetrazepam.

Tetrazepam has been described as an inductor of delayed type IV reactions, such as maculopapular exantema[4], Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome[4], and contact dermatitis[5]. The study of these patients usually did not show cross-reactivity among different benzodiazepines.[4]

Our patient presented with a clinical picture of anaphylaxis, which was reproduced after oral challenge. Interestingly, skin prick test results were negative initially but later turned positive after the development of a systemic reaction. This finding could be due to the local release of mediators from skin mast cells or the action of drug metabolites. Serum tryptase levels showed a progressive elevation and later a decrease, consistent with mast cell activation. These data strongly suggest a type I (IgE-mediated) mechanism.

Previous reports of type I reactions to benzodiazepines have not included studies to evaluate potential cross-reactivity. In our patient, skin testing and oral challenge performed with other benzodiazepines failed to show cross-reactivity, suggesting a selective pattern of sensitization.

Tetrazepam is similar chemically to diazepam, and this selective pattern of sensitization could be due to different metabolites.

In summary, we present a case of anaphylaxis to tetrazepam supported by serologic data. No evidence of cross-reactivity was found with other benzodiazepines, suggesting a selective IgE-mediated mechanism.

Juan Antonio Martínez-Tadeo, MD*
Eva Pérez-Rodríguez, MD*
Guacimara Hernández-Santana, MD*
José Carlos García-Robaina, MD, PhD*
Fernando de la Torre-Morín, MD, PhD*
*Hospital Universitario Ntra. Sra. De Candelaria
Allergy Service, Drug Allergy Unit
Santa Cruz de Tenerife, Canary Islands, Spain
arkanum78@hotmail.com

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