
CME review article

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Experimental models for the evaluation of treatment of allergic rhinitis

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Objective: To review the experimental models used for the clinical evaluation of treatments for allergic rhinitis.

Data Sources: Peer-reviewed clinical studies and review articles were selected from the PubMed database using the following relevant keywords: *allergic rhinitis* in combination with *efficacy*, *wheel and flare*, *nasal challenge*, *park*, *cat room*, or *exposure unit*. Regulatory guidance documents on allergic rhinitis were also included.

Study Selection: The authors' knowledge of the field was used to limit references with emphasis on recent randomized and controlled studies. References of historical significance were also included.

Results: Traditional outpatient studies are universally accepted in the evaluation of treatment for allergic rhinitis. Experimental models provide ancillary information on efficacy at different stages of treatment development. Skin histamine and allergen challenge, as well as direct nasal challenge with histamine and allergen, are often used as early steps in assessing drug efficacy. Exposure units, park settings, and cat rooms better approximate real life by drawing on the natural mode of allergen exposure and delivering the sensitizing allergen to allergic individuals in the ambient air. Park studies make use of allergens in the outdoors, whereas cat rooms and exposure units present the sensitizing allergens indoors, with the latter providing consistent predetermined allergen levels. Exposure unit and park studies are acknowledged for the determination of onset of action and are also suited to the measurement of duration of effect and other measures of efficacy. Onset and duration of effect are 2 important pharmacodynamic properties of antihistamines and nasal corticosteroids as determined by the Allergic Rhinitis and Its Impact on Asthma and the European Academy of Allergology and Clinical Immunology workshop group.

Conclusions: All challenge models serve as important instruments in the evaluation of antiallergic medications and provide additional information to complement traditional studies.

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INTRODUCTION

Allergic rhinitis is a common atopic disorder, estimated to affect 10% to 25% of the population, and epidemiologic studies indicate that the prevalence of this condition is increasing.¹ First-generation histamine₁ (H₁)-antihistamines

(eg, diphenhydramine and chlorpheniramine) were introduced for the treatment of allergic rhinitis more than 50 years ago and, although still in use, have been largely replaced by second-generation H₁-antihistamines (eg, loratadine, cetirizine, ebastine) and the newer second-generation antihistamines (eg, fexofenadine, desloratadine).² Antihistamine decongestant combinations and nasal corticosteroids (eg, fluticasone, mometasone) are also treatment choices, and a number of novel agents continue to be introduced and evaluated for treatment of allergic rhinitis.^{3,4} The Allergic Rhinitis and Its Impact on Asthma (ARIA) and the European Acad-

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emy of Allergy and Clinical Immunology (EAACI) workshop group has developed requirements for the evaluation of antiallergic medications being considered for development, which include evidence of efficacy, tolerability, lack of tachyphylaxis, and pharmacodynamic factors such as a rapid onset of action and a long duration of action with persistent clinical effects at the end of the 24-hour dosing period for once-daily drugs.⁵

To evaluate these diverse treatments, various experimental models for allergic rhinitis have been developed. The histamine-induced and allergen-induced wheal-and-flare models were the first to be recognized as means to demonstrate the suppressive activities of antihistamines. Later, nasal provocation studies using both histamine and allergen were developed for target sensitive evaluation. Since then, more clinically relevant models have been established, namely, park settings, cat rooms, and exposure units. All are recognized as valuable instruments to determine specific measures of efficacy of antiallergic medications. This article appraises each of these models in detail, indicating their strengths and weaknesses, and reviews selected studies of medications for allergic rhinitis that use these test systems. Peer-reviewed clinical studies and review articles were selected from the PubMed database using the following keywords: *allergic rhinitis* in combination with *efficacy*, *wheal and flare*, *nasal challenge*, *park*, *cat room*, or *exposure unit*. The authors' knowledge of the field was used to limit references with emphasis on recent randomized and controlled studies. References of historical significance were also included.

WHEAL-AND-FLARE MODEL

Histamine Wheal and Flare

The ability of medications to suppress the "whealing" reaction of the skin to localized histamine injection as an indicator of their antihistaminic activity was first described in 1950.⁶ Since then, the histamine wheal-and-flare model has been used to evaluate the antihistaminic effects of various medications as reported in numerous publications (some involving combined testing with allergen-induced wheal and flare). In addition to other efficacy measures, the onset and duration of action, relative potency, and homogeneity of response in a given population can be determined with this model.⁷

Histamine wheal-and-flare studies require a standardized epicutaneous skin prick (or intradermal injection) technique of histamine acid phosphate or histamine dihydrochloride and a defined area of skin for repeated measures, usually the volar surface of the forearm.⁸ The wheal that results from histamine injection is a consequence of increased skin blood flow and vascular permeability. The standard measure is the maximal diameter of the wheal, approximately 10 minutes after challenge, along with the diameter at right angles to the direction of this measure, with the mean of the 2 measurements, or a computed area, used for analysis.⁸ The flare response, which reflects the neurally mediated vasodilator effects of his-

amine, is more difficult to measure accurately but may be measured by a computerized planimetric system.⁸

Given the direct pharmacologic link between histamine and antihistamine, this test is often used as a first evaluation to determine antihistaminic properties of medications. Medication to be tested can be administered as a single dose or as multiple doses to achieve steady state, with skin test determinations extended during a set period. Serum drug levels can be measured in conjunction with serial wheal-flare assessments for pharmacokinetic studies.⁹

There are several advantages of histamine skin challenge, which include the acceptability of healthy volunteers. This test system is simple, inexpensive, well standardized, and easily reproducible, and its frequent use allows for comparisons across studies. A limitation of histamine skin challenge, however, is that it reproduces only the histamine phase of the cutaneous allergic reaction; therefore, any potential antiallergic effects of antihistamines on the early-phase response and the late-phase response cannot be evaluated. Nonetheless, because of the predominance of histamine in allergic reactivity, its ease in administration, and the reproducibility of results obtained from histamine-induced wheal and flare, this model is widely accepted and extensively used. Since 2000, numerous studies that used this technique have been published, with several focused on the comparison of 2 or more newer-generation antihistamines (Table 1).

Allergen Wheal and Flare

Skin testing with allergen is a more representative means to evaluate treatment responses than histamine. Allergen skin testing requires subjects with specific sensitivity to the allergen tested. Reactivity, however, is variable because of possible differences in antigenicity of different extracts and individual sensitivity. When testing medications, some clinical studies combine histamine wheal-and-flare responses together with allergen wheal-and-flare responses²⁷⁻²⁹ to obtain a broader depth of pharmacologic information. However, histamine is more commonly used for wheal-and-flare studies of antihistamines, since it is simple to administer and results are consistent.

Despite the obvious structural and functional differences that exist between the nasal mucosae and the skin, a pathophysiologic relationship exists between cutaneous wheal and flare and allergic rhinitis. Although results obtained from histamine and allergen skin challenge by their nature are not sufficient to determine clinical efficacy of treatments for allergic rhinitis, these models are useful in the screening of antihistamine efficacy and give generally reproducible results using a relatively small sample size.

DIRECT NASAL CHALLENGE

Nasal Histamine Challenge

Nasal histamine challenge involves the direct application of histamine onto the nasal mucosae, eliciting almost immediate itching, sneezing, and rhinorrhea, followed by nasal congestion, symptoms that closely resemble the early response to

Table 1. Review of Recent Double-blind, Randomized, Crossover, Placebo-Controlled Histamine-Induced Wheal-and-Flare Evaluations Comparing Single Doses of Newer-Generation Antihistamines*

Antihistamines studied and overall response (in decreasing order of potency)	Year of publication
Cetirizine > loratadine (in children)	2000 ¹⁰
Cetirizine (2.5, 5, 10 mg) > loratadine (10, 20, 40 mg)	2000 ¹¹
Ebastine (20 mg) > ebastine (10 mg) > cetirizine†	2000 ¹²
Levocetirizine > loratadine = placebo	2001 ¹³
Cetirizine = fexofenadine up to 4 hours; after 4 hours cetirizine > fexofenadine (120 mg = 180 mg)	2001 ¹⁴
Levocetirizine > fexofenadine > mizolastine > ebastine > loratadine	2002 ¹⁵
Ebastine (20 mg) > cetirizine > loratadine‡	2002 ¹⁶
Cetirizine > mizolastine	2002 ¹⁷
Cetirizine > epinastine	2002 ¹⁸
Cetirizine = ebastine = loratadine > fexofenadine (60 mg twice daily)†	2002 ¹⁹
Levocetirizine > desloratadine	2003 ²⁰
Ebastine (20 mg) > fexofenadine (120 mg)‡	2003 ²¹
Fexofenadine > loratadine	2003 ²²
Cetirizine > fexofenadine (30 mg) (in children)	2003 ²³
Levocetirizine > desloratadine	2003 ²⁴
Cetirizine > desloratadine	2004 ²⁵
Cetirizine = olopatadine (5 mg twice daily) > bepotastine (10 mg twice daily) > fexofenadine (60 mg twice daily)‡	2004 ²⁶

* Once-daily oral doses are cetirizine, 10 mg, desloratadine, 5 mg, ebastine, 10 mg, epinastine, 20 mg, fexofenadine, 180 mg, levocetirizine, 5 mg, loratadine, 10 mg, and mizolastine, 10 mg, unless otherwise stated. All medications were more potent than placebo unless indicated.

† Multiple doses tested.

‡ Single and multiple doses tested.

allergen.³⁰ These symptoms are elicited through sensory nerve activation (pruritus and sneezing), increased nasal mucosal blood flow (congestion), and increased secretion from goblet cells and increased vascular permeability (rhinorrhea). As in the skin, nasal histamine challenge does not produce the full pathophysiologic response of allergen challenge.

This testing method can be undertaken as in histamine skin test studies, with single-dose histamine challenges at repeated time points to evaluate onset and duration of action of antihistaminic medications. A histamine dose-response plot before and at a set time point after medication administration can also be used to evaluate the efficacy of a treatment relative to other medications.⁸

To perform this test, histamine is usually sprayed onto the nasal mucosae. The histamine dose range used is variable and appears to be dependent on the method of application, but the total dose of histamine is often not reported.^{31–34} The response is evaluated subjectively by ratings of the induced itch, sneeze, rhinorrhea, and nasal blockage. Objective measure-

ments include counting the number of sneezes and weighing anterior nasal secretions by collecting preweighed tissues after nose blowing. Measures of nasal congestion include peak nasal inspiratory flow and peak nasal expiratory flow, which can be determined in trained subjects with the use of flow meters.³⁵ Other measures make use of anterior³ and posterior rhinomanometry,³⁶ acoustic rhinometry,³⁷ whole-body plethysmography,³⁸ facial thermography,³⁹ and the combination of rhinostereometry and laser Doppler flowmetry.⁴⁰ Nasal lavage may be used to assay mediators, plasma proteins, and inflammatory cells.⁴¹ Commonly used markers of plasma protein exudation include total protein, albumin, and α_2 -macroglobulin, the latter being the most specific.^{8,42} Nasal cells can also be obtained for cytologic testing through brush sampling, nose blowing, or biopsy.^{43,44} The relative sensitivities of the various techniques for the direct or indirect measurement of nasal congestion or patency have been discussed, and the choice of technique depends on many factors, including relevancy, expense, experience, patient cooperation, and degree of invasiveness.^{32,34,45,46}

Nasal histamine challenge has been used to compare the efficacy of single doses of cetirizine, 10 mg, and loratadine, 10 mg, at 24 hours. The histamine dose-response curve for nasal obstruction as measured by posterior rhinomanometry was significantly lower after treatment with cetirizine compared with placebo, with no difference between loratadine and placebo.³⁶ However, pretreatment with 10 mg/d of loratadine for 1 week was shown to significantly reduce responses to nasal and maxillary sinus histamine challenge.³¹ Another study by Wang et al³³ demonstrated matching reduction of responses to nasal histamine challenges by both cetirizine and levocetirizine. Dextrocetirizine conversely produced a response similar to placebo, an indication that levocetirizine is the active enantiomer of cetirizine.

The tendency to produce tolerance or tachyphylaxis restricts the number of histamine challenges that can be undertaken in a single study population.⁴⁷ This and other limitations curtail the use of nasal histamine challenge in the evaluation of treatments for allergic rhinitis.

Nasal Allergen Challenge

In 1873, Blackley⁴⁸ showed that typical symptoms could be produced in allergic individuals by applying pollen to the nasal mucosae. Following further development, the direct nasal allergen challenge model has been applied to evaluate treatment of allergic rhinitis. Studies are typically conducted outside pollen season when subjects are asymptomatic, with at least 1 week between provocations to minimize the "priming effect" and achieve stable baseline symptoms.⁴⁹

There are several techniques used to deliver allergen to the nasal mucosae, some resulting in localized placement of the allergen, whereas others permit a wider distribution. Allergens can be administered to the nose in aqueous solution by dripping, pipette, nasal pool device, or pump spray.⁵⁰ Allergens may also be administered by nebulization as powder, as a solution adsorbed on a paper disk, or as pollen grains

encapsulated with lactose.⁵¹ Local irritation and discomfort may be produced with repeated stimulation,⁴⁷ the extent of which depends on the delivery technique.

The amount of allergen used for nasal challenge is individualized because of the variability in interindividual reactivity and is often estimated using a titration procedure to attain a tolerable, repeatable symptom-producing dose,^{52,53} in turn dependent on allergen preparation and delivery techniques and the purpose of the investigation.⁵⁴ However, the amount of allergen may be inconsistent and excessive.⁵¹ Not all commercial allergen extracts are standardized, and therefore they may not accurately represent the native allergen to which the subject is sensitive.⁵¹ In addition to standardization, the stability and purity of an allergen extract are required.⁵⁰ Preservatives in the extract may induce nonspecific nasal reactions and should be controlled for. For both histamine and allergen nasal challenge, it is also important to allow time for equilibration of the nasal mucosae with environmental conditions of the laboratory and to control for the effects of the delivery system.^{47,55}

The acute nasal allergen challenge model uses either a single provocation or a series of successive provocations of increasing allergen dose separated by at least 10 minutes.⁵⁰ As described for nasal histamine challenge, several subjective and objective methods can be used to evaluate response to nasal allergen challenge.

Allergic symptoms and mediators associated with the early-phase response have been decreased by a variety of antihistamines, including topical and oral H₁-antihistamines (azelastine,⁵⁵ cetirizine,⁵⁶ desloratadine,^{57,58} ebastine,⁵⁹ levocetirizine,⁵⁸ mizolastine,⁶⁰ loratadine,^{56,61} and terfenadine^{61–63}) using this model. In select studies, a few antihistamines decreased mediator release and inflammatory cell influx associated with the late-phase response.^{64,65} Alternatively, the release of mediators, inflammatory cells, and other components of the late-phase response have been shown to be attenuated by pretreatment with intranasal corticosteroids (budesonide,⁶⁶ fluticasone,⁶⁷ and mometasone⁶⁸) using this model. Other antiallergic treatments tested include subcutaneous⁶⁹ and sublingual immunotherapy⁷⁰ and intranasal heparin.⁷¹

It has been suggested that the lack of long-term exposure is an important limitation of direct nasal allergen challenges, which is in contrast to the relatively continuous allergic reactivity that occurs in the natural environment.^{51,72} Nevertheless, natural allergen exposure in fact is not continuous but intermittent as a consequence of a number of factors, including weather, normal diurnal variations of pollens, and variable activities in daily life.⁴⁹

Direct nasal allergen challenge models have also been developed to emulate an “artificial” pollen season by challenging subjects with allergen once daily for 7 to 8 days.⁷³ Around-the-clock symptoms (ie, 12 and 24 hours after challenge) occur during the latter portion of the challenge series,^{35,52} and inflammatory changes are similar to those observed in natural disease.⁷³ Evidence of a dose-response

relationship for intranasal corticosteroids has been shown using this repeated allergen challenge model.^{35,52} It has also been used in the evaluation of roflumilast, a novel phosphodiesterase 4 inhibitor.³ In this study, 25 subjects received oral roflumilast, 500 µg/d, for 9 days or placebo in a double-blind crossover design. Intranasal allergen provocation with atomized pollen extract solution was performed daily from day 3 to day 9 of treatment. Subjective ratings of congestion were significantly lower in the active treatment arm from day 4 onward, whereas rhinal airflow (evaluated by rhinomanometry), itching, and rhinorrhea were improved compared with placebo by day 9.

Other Nasal Challenge Models

Adenosine monophosphate has been identified as a nonspecific means to reproduce symptoms of allergic rhinitis. The nasal adenosine monophosphate challenge model has been used to evaluate the efficacy of various treatments for allergic rhinitis, such as corticosteroids,⁷⁴ an antihistamine alone and in combination with a leukotriene receptor antagonist,⁷⁵ and the herbal remedy butterbur.⁷⁶ Mannitol has also been recently introduced as a challenge agent.⁷⁷ The relationship between nonspecific nasal hyperreactivity produced by these challenge agents and allergic rhinitis symptoms induced by allergen is not well understood, casting doubt on their clinical relevance.

The method of repeated nasal challenge using allergen as the provoking agent best approximates the clinical events of allergic rhinitis. Although the direct nasal challenge model offers reproducibility and experimental control and may detect small differences between treatments in comparatively low numbers of subjects,⁵⁸ it is associated with a number of technical problems. The unnatural mode of presenting allergens also limits its role as a challenge model.

NATURAL EXPOSURE MODELS

Traditional outpatient trials, usually of multicenter design, are considered clinically relevant, because allergic individuals participating in these trials are exposed to the sensitizing allergen(s) in their natural environment as part of their day-to-day life, representing the usual conditions under which the treatment is given. Some researchers believe that only settings based on naturally occurring disease have true relevance.⁸ Subjects in traditional studies are provided with medication and instructions for its administration and for the completion of subjective and/or objective assessments of allergic rhinitis symptoms. These studies, however, are associated with irregular compliance with medication dosing regimens and incomplete and untimely symptom assessments, and there is also a need to conduct the trial during the pollen season, when the variability in pollen exposure becomes a factor in symptom expression and interpretation of results. The variability of pollen exposure and other limitations inherent in traditional outpatient seasonal allergic rhinitis (SAR) trials have been acknowledged in the US Food and Drug Administration (FDA) guidance and the European Med-

icines Agency guideline for the clinical development of medicinal products for the treatment of allergic rhinitis.^{78,79} To limit the problems associated with insufficient pollen levels, traditional trials are usually scheduled during the anticipated period of peak pollen exposure when symptoms would be expected to occur regularly during the study.⁸ This presents logistical problems, especially in large multicenter trials, as reported in a recent publication in which pollen levels were highly variable between sites and among 3 separate studies conducted during consecutive fall seasons, significantly affecting the evaluation of treatment.⁸⁰ Furthermore, individual exposure is unavoidably influenced not only by weather factors but also by personal factors, such as frequency and duration of outdoor exposure.⁴⁹

Traditional trials provide information on general measures of efficacy but because of previously stated limitations are unable to accurately determine specific measures such as onset and duration of action. Outdoor (or park) settings and cat room studies address some of these concerns, but exposure units deliver consistent allergen levels. Unlike skin and direct nasal challenge models, these systems draw on the natural presentation of allergen to study participants.

The FDA has acknowledged both park and exposure unit studies as systems of evaluation of onset of action of antiallergic medications for SAR in its Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products.⁷⁸ Exposure unit studies may also be used to evaluate antiallergic medications for the prophylactic treatment of SAR,⁷⁸ taking advantage of their ability to deliver pollen levels representative of the peak of allergy season, unreliably encountered in traditional and park studies.

Outdoor (Park) Settings

In 1979, Connell⁸¹ conducted the first clinical trial in which subject response to medication was evaluated in a structured outdoor setting during ragweed season to enable control and equalization of as many variables as possible. He accomplished this by standardizing the test environment, time of treatment, time of symptom reports and objective measurements, subjects' activities, and oral intake. Using this outdoor setting, he designed a study to evaluate the efficacy of azatadine, pseudoephedrine, and their combination for relief of "hay fever" symptoms. Subjects reported to the study site situated on the lawn of a motel for 2 consecutive 8-hour days. They recorded their symptoms at hourly intervals and were randomized to supervised treatment according to symptom severity. In this study, azatadine relieved allergic rhinoconjunctivitis symptoms excluding nasal congestion, pseudoephedrine relieved nasal congestion only, and the combination relieved all symptoms.⁸¹

Despite the outdoor challenge model's obvious advantages for the evaluation of treatment of allergic rhinitis, no outdoor studies were conducted until 1990. Since then, 13 randomized, double-blind, placebo-controlled, outdoor challenge studies have been conducted typically in park settings intended to have sufficient naturally occurring pollen during the

appropriate season. The main objectives of park studies have been to evaluate the onset and duration of action of various antiallergic treatments. A variety of antiallergic treatments have been tested, including antihistamines, antihistamine-decongestant-analgesic combinations, nedocromil, mometasone, an investigational leukotriene D₄ receptor antagonist, and an intranasal Syk-kinase inhibitor (Table 2). The duration of park studies has ranged from a minimum of one 2-hour day to a maximum of 2 consecutive 10-hour days.

Although park studies have been able to provide controls not possible in traditional studies by ensuring the timely completion of symptom assessments, monitoring medication compliance, and restricting subjects' activities and oral intake, they have inherent limitations. Foremost is that equal and consistent pollen exposure cannot be ensured even in localized geographic areas, which is compounded when there is more than one cohort within a site or multiple sites. This limitation is exemplified by a 5-site study in which sites that had higher pollen levels yielded a different time for onset of action for the same treatment.⁹¹ Another difficulty is that even for individual subjects, there is a diurnal variation in pollen levels in these settings. This was demonstrated by a park study in which a large variation in pollen levels ranging from less than 100 to more than 3,000 grains/m³ was observed throughout the day, leading to concerns regarding the effect of pollen on symptom intensity and thus response to medication.⁸³ Unaccountably, not all park studies report pollen counts as seen in 4 of 14 published studies,^{82,85,86,89} and in studies reporting pollen counts, there is little information on pollen sampling methods or pollen type(s).^{90,93}

A criticism of park studies (one that could equally apply to exposure unit and cat room studies in which subjects are gathered together in a similar environment) is the mutual expectation of a beneficial effect of therapy, leading to a greater placebo response.⁸ The placebo effect is universal, occurring in all clinical trials of allergic rhinitis, including traditional studies.⁹⁵⁻⁹⁷ In traditional studies, the placebo effect may be explained in part by the natural reduction in seasonal pollen levels.^{8,80}

Other limitations of the park study model include the requirement for studies to be conducted during the pollen season in variable weather conditions, which would not only influence pollen levels but also affect accuracy of subjective assessments of symptoms, a problem exaggerated when other sites are included. Furthermore, since weather conditions and pollen levels are unpredictable, the duration of park studies is restricted, thus limiting safety data and other information readily derived from longer studies.

Cat Rooms

Live cats in an enclosed room have been used as an antigen delivery vehicle for clinical testing in Southampton, England,⁹⁸ Johns Hopkins University in Baltimore, MD,⁹⁹ and most recently in Los Angeles, CA.¹⁰⁰ All sites present a closed environment capable of holding cats for testing cat-sensitive subjects. This results in a natural allergen exposure

Table 2. Overview of Medications Studied Using the Outdoor (Park) Model*

Medications	Duration of pollen exposure	Year of publication
Chlorpheniramine-pyrilamine-phenylephrine (8 mg/25 mg/25 mg twice daily) for 2 days	2 days at 8 hours per day	1990 ⁸²
Nedocromil (1% intranasal, 4 times daily) for 2 days	2 days at 10 hours per day	1993 ⁸³
Acrivastine (8 mg)†	Up to 2 hours	1994 ⁸⁴
Azelastine (0.1% intranasal, 0.55 mg vs 0.55 mg every 12 hours) vs chlorpheniramine (12 mg every 12 hours) for 2 days	2 days at 8 hours per day	1994 ⁸⁵
Azelastine (0.1% intranasal, 0.24 mg every 12 hours vs 0.48 mg vs 0.48 mg every 12 hours) vs chlorpheniramine (12 mg every 12 hours) for 2 days	2 days at 8 hours per day	1994 ⁸⁶
Investigational leukotriene D ₄ receptor antagonist (ICI 204, 219; 10, 20, 40 mg vs 100 mg)	2 days at 8 hours per day	1995 ⁸⁷
Cetirizine (10 mg) vs loratadine (10 mg) for 2 days	8.5 hours (day 1), 8 hours (day 2)	1996 ⁸⁸
Azelastine (0.5 mg twice daily) for ≥7 days ± azelastine (intranasal, 0.55 mg every 12 hours) for 2 days	2 days at 9 hours per day	1997 ⁸⁹
Mometasone (intranasal, 200 µg)	12 hours	1999 ⁹⁰
Acrivastine-pseudoephedrine (8 mg/60 mg) vs loratadine-pseudoephedrine (5 mg/120 mg)	7 hours	2000 ⁹¹
Clemastine-pseudoephedrine-acetaminophen (0.68 mg/60 mg/1,000 mg twice daily) vs pseudoephedrine-acetaminophen (60 mg/1000 mg twice daily)	9.5 hours	2003 ⁹²
Syk-kinase inhibitor (R112; intranasal, 6 mg twice daily) for 2 days	10 hours (day 1), 9 hours (day 2)	2005 ⁹³
Cetirizine (10 mg) vs fexofenadine (60 mg twice daily) vs loratadine (10 mg) for 2 days	2 days at 6 hours per day	2005 ⁹⁴

* All studies are of randomized, double-blind, placebo-controlled, and parallel-group design. Medications were administered orally as single once-daily doses unless otherwise indicated.

† Hayfield was used as outdoor setting, and number of doses and duration of exposure depended on response.

system, but live cat sources of antigen result in widely variable airborne levels of Fel d 1. In particular, Fel d 1 levels were reported to range from 35 to 37,967 ng/m³ in a single study⁹⁹ and represent airborne levels that are 10- to 50-fold higher than in a typical home with cats.¹⁰¹ Thus, cat room exposures are intense and designed to be of short-term duration (ie, up to 1 hour).

Cat rooms have been used to investigate the value of acoustic rhinometry¹⁰² and to evaluate the efficacy of various antiallergic medications, including intranasal steroids (triamcinolone),⁹⁹ T-cell reactive peptides,¹⁰³ immunotherapy,⁹⁸ and leukotriene antagonists.^{100,104,105} Although the efficacy of medications in allergic rhinitis or allergic asthma has been demonstrated in cat room studies, concerns have been raised about the intensity of allergen exposure and its effect on treatment.¹⁰⁴

Cat rooms nevertheless provide natural allergen exposure in easily identifiable environments and allow subjective and/or objective assessments of response. Although this model is appealing for ease in development and its natural exposure, its application is limited by the small number of subjects that can be evaluated simultaneously and the pronounced variability of antigen levels within the challenge area. As a consequence of the possibility of severe allergic reactivity and the resultant limited duration of exposures, this

model is unsuitable for determining onset and duration of action of medications.

Exposure Units

The development of exposure units as a model system to test antiallergic medications has arisen out of the need for a clinically relevant setting of extended periods of consistent predetermined levels of allergen exposure. These systems use controlled allergen delivery to activate allergic symptoms in sensitive individuals, and their unique design allows for year-round, indoor evaluation.

During the past 2 decades, different types of exposure units, sometimes referred to as allergen challenge chambers, have been developed. A pollen challenge environment was first described in a pilot study by Davies in 1985.¹⁰⁶ This challenge system consisted of a transparent polythene (upper half) and blockboard (lower half) box designed to hold one person at a time. Grass pollens at concentrations ranging from 1,000 to 50,000 grains/m³ were delivered by passing a stream of compressed air through grass pollen-impregnated gelatin capsules while air was circulated in and out of the box using a circulation pump. Much higher pollen concentrations were required to elicit a positive response within the maximum 30-minute exposure, likely due to the higher symptom threshold selected for this study. Although the grass pollen concen-

trations used in exposure units in the present day fall within the lower end of the range reported by Davies, these and other allergen levels used by exposure units are frequently perceived to be higher than atmospheric levels.^{8,107} Atmospheric levels may be underestimated by commonly performed sampling at rooftop heights as evidenced by an 11- to 26-fold increase in grass pollen concentrations measured at 1.5 m above ground level compared with 15 m.⁸⁴ Additionally, environmental pollen levels are normally reported as a 24-hour average, further contributing to underestimation of peak levels as a consequence of lower pollen levels overnight.

Exposure units now consist of specialized facilities for simultaneous exposure of subjects and advanced monitoring of airflow and allergen delivery in a comfortable setting. Consequently, these systems require expensive, originally designed equipment, technical expertise, and a safe venue. Currently, there are 5 exposure units worldwide (ie, Austria, Canada, Denmark, Germany, and the United States), which have studies published in peer-reviewed journals. These exposure units use ragweed, grass and birch pollens, or house dust mite as challenge allergens.

In 1987, Horak and Jäger¹⁰⁸ first reported use of the Vienna Challenge Chamber (VCC), in which up to 9 people could be exposed to constant levels of grass pollen for several hours. Later, the VCC circulated dust mite allergen¹⁰⁹ and birch pollen.¹¹⁰ The VCC has been used to study the efficacy of topical and oral antihistamines, combination products, and immunotherapy (Table 3). The evaluation of the conjunctival vascular reaction by digital imaging techniques,¹²¹ rhinore-sistometry vs rhinomanometry,¹²² and a few pathophysiologic

studies have also been conducted in this setting.^{123,124} Allergen exposures in VCC studies last from 2 hours to a maximum of 2 successive 6-hour days. A crossover design is frequently used to overcome limitations based on an expanded maximal seating of 14 subjects at a time,¹¹⁸ with the largest number of subjects in any one trial conducted in the VCC most recently increased to 94.¹²⁰

The Environmental Exposure Unit (EEU) was developed at about the same time in Kingston, Ontario, based on technology derived from chamber challenge studies of urea formaldehyde foam insulation.¹²⁵ The EEU is a large, climate-controlled room in a hospital setting with adjacent medical support. Cohorts of up to 160 subjects at a time can be accommodated in the EEU, where they may undertake normal day-to-day activities, such as reading, watching television, or social interaction. While subjects are asked to remain as much as possible within the seating area where the pollen concentration is regularly monitored, washroom breaks, stretching, and access to the back of the room for food or refreshments are allowed. These activities are not unlike real-life experiences, yet facilitate continuous medical monitoring, regular instructions, and ready access to medical personnel to ensure timely intercommunication and care.¹²⁶

For a given study population numbering up to 600, which may be composed of multiple cohorts, each cohort, and each subject within a cohort, is exposed to consistent predetermined levels of pollen throughout a study. Levels of ragweed pollen from 200 to 10,000 grains/m³ have been tested for extended periods in the EEU, but currently studies use a mean $\pm$ SD target pollen concentration of 3,500 $\pm$ 500

Table 3. Overview of Medications Studied Using the Vienna Challenge Chamber*

Medications	Duration of allergen exposure†	Year of publication
Dimethindene (4 vs 8 mg)	4 hours	1993 ¹¹¹
Astemizole (10 mg)	4 hours	1993 ¹¹²
Dimethindene (4 vs 8 mg)	4 hours	1994 ¹⁰⁹
Astemizole-pseudoephedrine (10 mg/240 mg) vs loratadine-pseudoephedrine (5 mg/120 mg) twice daily for 3 days	4 hours (day 1), 3 hours (day 3)	1996 ¹¹³
Dimethindene (intranasal, 0.14 vs 0.56 mg) vs azelastine (intranasal, 0.56 mg)	4 hours	1996 ¹¹⁴
Cetirizine-pseudoephedrine (5 mg/120 mg) twice daily for 7 days	7 hours (day 1), 3 hours (day 7)	1998 ¹¹⁵
Birch pollen immunotherapy (sublingual, 28-day dose escalation phase followed by 3-month dose maintenance phase)	2 hours (day 1, pre-escalation), 2 hours (day 2, postmaintenance)	1998 ¹¹⁰
Dimethindene (0.1% intranasal, 0.28 mg every 12 hours)	4 hours	2000 ¹¹⁶
Desloratadine (5 mg) for 7 days	6 hours (day 7)	2002 ¹¹⁷
Desloratadine (5 mg) for 7 days	6 hours (day 7)	2003 ¹¹⁸
Levocetirizine (5 mg) vs loratadine (10 mg) for 2 days	2 days at 6 hours per day	2004 ¹¹⁹
Levocetirizine (5 mg) vs fexofenadine (120 mg)	4 hours (day 1), 6 hours (day 2)	2005 ¹²⁰

* Only studies of randomized, double-blind, and placebo-controlled design were included. Medications were administered orally as single once-daily doses unless otherwise indicated.

† Duration of allergen exposure is to be multiplied by the number of treatment groups (including placebo), since all studies are of crossover design (except for immunotherapy trial).

grains/m³.¹²⁶ This ragweed pollen level, which is equated with documented peak outdoor levels,^{83,127,128} produces the full spectrum of symptom severity from mild to severe in allergic patients, without affecting nonallergic persons.¹²⁹ Seven Rotorod samplers distributed throughout the seating area measure and confirm that pollen levels are consistent by sampling for 30 seconds at 30-minute intervals during the challenge period.¹²⁶

Once subjects are screened and deemed acceptable for entry into a study, they undergo a series of priming sessions to awaken and establish an adequate level of allergic reactivity according to predefined symptom scores. Individual response to priming is variable and dependent not only on the time of the year but also on other factors, such as concomitant allergen exposure and allergic sensitivity.¹³⁰ Subject self-rated symptom scoring is the preferred and most commonly used measure of efficacy, but exposure unit settings are also amenable to various methods of symptom evaluation. This versatility is particularly useful for the exploration of new end points and innovative techniques, which cannot be readily performed in other systems.

The EEU has been used to substantiate the priming effect of antigen exposure and the onset of allergic symptoms, as well as to determine efficacy of ragweed immunotherapy¹²⁹ and various measures of medication efficacy, including the onset and duration of action of antihistamines and nasal corticosteroids (Table 4). In addition, the burden of treatment of SAR on vigilance and cognitive function has been evaluated in the EEU,¹⁴⁰ as well as the impact of controlled allergen challenge on quality of life¹⁴¹ and quality of life as a predictor of placebo response.¹⁴²

The validity and reproducibility of study results within the EEU, including the accuracy of subject self-reporting of symptoms, have been recently confirmed in 2 trials identical in design, which were intended to evaluate the comparative onset of action of cetirizine and loratadine. In the first trial undertaken in 1995, allergic subjects (n = 202) were exposed to ragweed pollen for 7 and 6 hours on 2 consecutive days,

where they received in a randomized fashion 10 mg of cetirizine, 10 mg of loratadine, or placebo each day. Cetirizine produced a 37.4% mean reduction in major symptom complex scores overall vs 14.7% with loratadine and 6.7% with placebo. Onset of action as evaluated by reduction in major symptom complex and total symptom complex scores vs placebo was evident within 1 hour for cetirizine and 3 hours for loratadine.¹³⁴ The second study, which involved 360 subjects, was completed in 1999 and showed identical onset of action and comparable efficacy.¹³⁶ Unlike other natural exposure models, virtually all aspects of exposure unit studies, including allergen concentrations, can be replicated, enabling confirmation of results. However, differing study designs, including methods of evaluation, can have an effect on the determination of time to onset of action.^{143,144}

In EEU trials, the treatment evaluation phase is typically of 1 to 2 days' duration involving 5 to 7 hours of daily pollen exposure, but exposure periods have ranged from 3 hours up to a maximum of 14 hours.¹³⁵ A perceived limitation of exposure units is that pollen exposure is not "natural" compared with in-season at-home (or traditional) studies.¹⁴⁵ Actually, subjects who participate in these trials equate this experience with real life and report that symptoms in the EEU are similar to those experienced during the pollen season. These observations were recently confirmed in a survey where subjects completed an evaluation of their allergic symptoms in ragweed season and again while participating in a trial conducted in the EEU.¹⁴⁶

In 1996, an exposure chamber delivering house dust mite aerosols for single subject challenge was developed by Rønborg and colleagues¹⁴⁷ at the National University Hospital in Copenhagen. Exposure to minor amounts of Der p 1 allergen (1,200 ng) elicited allergic symptoms in allergic asthmatic patients but not in healthy individuals, whereas allergic asthmatic patients were not reactive to placebo exposure. The Atlanta allergen exposure unit, designed by Berkowitz et al, is a large-scale controlled challenge unit that circulates ragweed pollen and seats up to 150 subjects. Studies in this unit

Table 4. Overview of Medications Studied Using the Environmental Exposure Unit*

Medications	Duration of allergen exposure†	Year of publication
Triamcinolone (intranasal, 400 µg) for 7 days	3 hours for 7 days	1996 ¹³¹
Terfenadine (60 mg) vs astemizole (10 mg) vs cetirizine (10 mg) vs loratadine (10 mg)	6 hours	1997 ¹³²
Fexofenadine (60 vs 120 mg)	6 hours	1997 ¹³³
Cetirizine (10 mg) vs loratadine (10 mg) for 2 days	7 hours (day 1), 6 hours (day 2)	1998 ¹³⁴
Budesonide (intranasal, 64 vs 256 µg)	14 hours	2000 ¹³⁵
Cetirizine (10 mg) vs loratadine (10 mg) for 2 days	7 hours (day 1), 6 hours (day 2)	2001 ¹³⁶
Cetirizine (10 mg) vs fexofenadine (180 mg) for 2 days	7 hours (day 1), 5 hours (day 2)	2004 ¹³⁷
Desloratadine (5 mg) vs levocetirizine (5 mg) for 2 days	7 hours (day 1), 6 hours (day 2)	2004 ¹³⁸
Cetirizine (10 mg) vs fexofenadine (180 mg)	10 hours	2005 ¹³⁹

* Only studies of randomized, double-blind, placebo-controlled, and parallel-group design were included. Medications were administered orally as single once-daily doses unless otherwise indicated.

† Does not include allergen exposure during priming and/or placebo run-in phases.

have evaluated the onset of action and efficacy of the combination of fexofenadine and pseudoephedrine in the treatment of symptoms of SAR^{148,149} and the effects of allergic rhinitis on vigilance and cognitive function.¹⁵⁰ The most recently developed exposure unit is located in Hannover, Germany, within the Fraunhofer Institute of Toxicology and Experimental Medicine and is of smaller capacity (18 volunteers). This unit has been described in a study in which subjects with SAR were exposed to grass pollen¹⁵¹ and was recently used in a dose-ranging evaluation of the efficacy of loteprednol etabonate nasal spray.¹⁵²

Since exposure unit and park studies have been mostly designed to evaluate onset and duration of action of antiallergic treatments, they are mainly of short-term duration, usually single dose or 2 doses tested during a 2-day period. Evidence of onset of action is particularly relevant, since intermittent or as needed use is common, in patients taking antiallergic drugs,¹⁵³ even when medications are prescribed for regular use.¹⁵⁴ Clinical trials of newer antihistamines have established efficacy in daily use and intermittent or as needed use. For patients with intermittent rhinitis, antihistamines are listed among the first-line choices,¹⁵⁴ and in such situations, an agent with a short onset of action after a single dose is preferable.^{7,154} Nasal glucocorticosteroids, traditionally assumed to require days before providing symptomatic relief, have been shown to act as early as 7 hours in an exposure unit study, with objective evidence of earlier onset.¹³⁵ In addition to onset of action, the ARIA/EACI workshop group has recommended the evaluation of duration of action, another important pharmacodynamic property of an antiallergic medication,⁵ which is reliably determined in exposure unit studies.

Exposure units and, for that matter, cat rooms are not limited to short-term studies but have been designed to evaluate medications under steady-state conditions (ie, 1- to 2-week period) with subjects taking medication on a daily basis.^{105,118,131,152} This type of design is particularly suited to exposure unit studies, since subjects have consistent allergen exposure on designated dates during an extended treatment period.

COMPARABILITY OF MODELS

How do the different experimental models compare in their evaluation of the efficacy of medications for the treatment of allergic rhinitis? This question may be addressed by reviewing randomized, double-blind, placebo-controlled, comparative studies of cetirizine, 10 mg, and fexofenadine, 120 or 180 mg, in once-daily dosing regimens. Studies of cetirizine and fexofenadine were selected for comparison, since most of the experimental models have been used to directly compare these 2 commonly used antihistamines. With single-dose administration, both cetirizine and fexofenadine were shown to possess a similar onset of action and magnitude of effect in the suppression of histamine wheal-and-flare responses within the first 4 hours of dosing¹⁴ and a similar onset of action and efficacy in relieving rhinitis symptoms in ragweed allergic individuals within the first 5 hours of an exposure

unit study.¹³⁷ When the end of the 24-hour dosing interval was examined, cetirizine demonstrated a better duration of action than fexofenadine in the histamine wheal-and-flare study¹⁴ and produced better symptom relief 21 to 24 hours after dosing in the exposure unit study.¹³⁷ In a recently completed follow-up study also conducted in an exposure unit, cetirizine was shown to provide better symptom relief than fexofenadine during the 5- to 12-hour postdose period.¹³⁹ These symptom responses mirrored the time course of wheal-and-flare inhibition comparing cetirizine and fexofenadine.¹⁴ No distinguishable effects, however, were observed between cetirizine and fexofenadine or 3 other antihistamines in a study that used histamine and grass pollen wheal-and-flare and grass pollen nasal provocation models, a finding likely attributable to the small sample size ($n = 12$).¹⁵⁵ In a recent, 2-day park study conducted in Japanese cedar pollen season in Osaka, Japan, cetirizine, 10 mg, was claimed to relieve SAR symptoms better than fexofenadine, 120 mg, and loratadine, 10 mg, based on its superiority relative to placebo.⁹⁴ However, since fexofenadine was administered in 60-mg doses, twice a day, this study has not been included in this comparison of experimental models.

In contrast to the results obtained from the experimental models, a traditional, multicenter, outpatient SAR study showed that 2-week treatment with once-daily cetirizine, 10 mg, or fexofenadine, 120 or 180 mg, was equally efficacious in relieving SAR symptoms. In this study, both antihistamines demonstrated similar reductions in 24-hour instantaneous and reflective symptom scores during the 2-week period indicative of full 24-hour protection.¹⁵⁶ However, a comparative analysis of results obtained from the histamine wheal-and-flare and exposure unit models and the traditional study is impossible, since the multicenter trial was not designed to evaluate the 24-hour dosing interval after a single dose. The combined results from all of these studies showed that once-daily treatment with cetirizine (10 mg) or fexofenadine (120 or 180 mg) is similarly efficacious during a 2-week period, whereas a single dose of cetirizine produces more symptom relief than fexofenadine in the 5- to 12-hour period and at the end of the 24-hour dosing interval but similar efficacy for the first 5 hours after dosing. Experimental models thus provide specific supplementary information not readily obtained by traditional multicenter trials, but given their usual short duration, safety information is limited.

The similarity in results obtained from the histamine wheal-and-flare model and the exposure unit setting is reflected in the aforementioned studies^{14,137,139} and has been observed in other single-dose antihistamine studies.¹⁵ These similarities indicate that antihistaminic activity plays a predominant role in the symptomatic relief of allergic rhinitis during the 24-hour dosing interval, meanwhile supporting the role of histamine wheal and flare as a preliminary test of antihistamine efficacy.

Neither pharmacodynamic results^{30,157} obtained in wheal-and-flare studies nor the results of direct nasal challenge studies¹⁵⁵ are always predictive of the clinical efficacy of

H₁-antihistamines during SAR. This is not unexpected, since results obtained from models using single doses of medication cannot be extrapolated to traditional SAR studies, which evaluate medications at steady state and thus are designed to be of longer duration. Determination of the validity of experimental models in predicting clinical efficacy of antiallergic treatments requires a comparison of carefully designed studies, which measure the same end points and timeframes and use adequate statistical power to detect differences. Failure to take these factors into consideration may lead to erroneous conclusions.^{56,157}

The existence of studies of similar design and with similar objectives presents a unique opportunity to directly compare clinical findings obtained from various experimental models. The following compares the exposure unit and the park setting, since both models were used in 2-day, placebo-controlled, randomized, double-blind, parallel-group studies that evaluated the same treatment regimens (single doses of cetirizine, 10 mg, and loratadine, 10 mg) and used the same symptom rating scales, symptom qualifying scores, and efficacy variables.^{88,134,136} In addition, randomized subjects in all 3 studies started treatment with a similar symptom level at baseline as confirmed by comparable mean major symptom complex scores.

As already discussed, cetirizine demonstrated an earlier onset of action (1 hour vs 3 hours) and produced superior symptom relief compared with loratadine and placebo, whereas loratadine produced greater symptom relief than placebo in both EEU studies. In contrast, in the park study, the symptom response curve for the loratadine group was similar to that of placebo. Cetirizine produced better symptom relief than loratadine and placebo at most time points. A time of onset of action of 2 hours was claimed for cetirizine based on a significant difference vs loratadine and not placebo, which was not maintained at the next evaluable time point of 3 hours. In addition, 5 hours was the first time point when cetirizine demonstrated significant symptom reduction vs placebo, which was not maintained at the next evaluable time point of 6 hours.

Why did this park study not show the same clinical findings as the EEU studies? One possible explanation may be that differences between treatment and placebo were affected by the variability of pollen levels between the 2 park settings in San Diego and Iowa City. The average daily pollen counts of 34 grains/m³ and 210 grains/m³ during the 2-day study period represented a 6-fold difference between the 2 sites. Insufficient exposure to pollen at one site may have also been a factor in the high placebo response and the resultant failure to detect differences between loratadine and placebo.

FUTURE DIRECTIONS

The availability of several experimental models to evaluate efficacy of antiallergic medications for allergic rhinitis enables a wide range of assessments, depending on the state of development of the medication and the information required. Valuable preliminary evidence of efficacy may be obtained

by determining suppressive effects in histamine and allergen skin test challenges. Evidence of response may be followed by further tests of efficacy using direct nasal histamine or allergen challenge. These tests may be followed by traditional multicenter trials, providing further indication of long-term efficacy along with important safety data in a clinical setting. With information indicating sufficient efficacy and safety to proceed, desired pharmacodynamic properties such as onset and duration of action would be determined by park settings and exposure units, comparing a treatment with placebo, over a dose range, or with other medications. Exposure units would also give additional information on steady-state efficacy through repeated exposures during extended treatment periods.

As yet there is no unifying system that can directly compare one experimental model with another in terms of their relative abilities to accurately test the efficacy of antiallergic treatments. Results obtained from the various experimental models must be considered in light of differing study designs, including varied parameters for symptom and efficacy evaluation, statistical plans, and timeframes. The availability of these models is an opportunity for rigorous examination in a prospective manner by standardizing as many parameters as permissible through the unique features of each model using short- and longer-term treatment regimens and comparing the results to those obtained in traditional trials. Ultimately, a consensus on the standardization of study designs should allow unimpeded interpretation of results between models in addition to which there would be a better understanding of each model and its respective suitability for the evaluation of antiallergic treatment.

CONCLUSIONS

The evaluation of antihistamines and other antiallergic medications used in the treatment of allergic rhinitis may be undertaken by a number of experimental models. These consist of histamine and allergen skin test challenges, direct histamine, and allergen nasal challenge, alone or in combination. The more clinically relevant models are cat rooms, park settings, and controlled allergen delivery systems provided by exposure units, the latter 2 models being suited to the determination of specific measures of efficacy, such as onset and duration of action of antiallergic treatments. Experimental model studies supplement traditional studies, considered to be the standard of treatment evaluation by providing a more comprehensive clinical profile of test medication.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

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CME Examination

1–5, Day JH. 2006;96:263–278.

CME Test Questions

1. What is the universally accepted standard method for the evaluation of the efficacy of antiallergic medications for allergic rhinitis?

- a. traditional outpatient trial
- b. wheal-and-flare model
- c. direct nasal challenge
- d. outdoor (park) setting
- e. exposure unit

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2. Why is histamine wheal and flare commonly used in the evaluation of antiallergic medications for allergic rhinitis?
 - a. it is well standardized
 - b. it is inexpensive
 - c. it gives reproducible results obtained from a relatively small sample size
 - d. histamine plays a major role in the allergic response
 - e. all of the above
 3. What are some limitations of the traditional outpatient trial in the evaluation of treatment for allergic rhinitis?
 - a. irregular medication compliance
 - b. incomplete and untimely symptom assessments
 - c. variable allergen exposure
 - d. inability to predict peak pollen season
 - e. all of the above
 4. Which important variable cannot be controlled in the outdoor (park) model?
 - a. time of subject arrival
 - b. pollen levels
 - c. level of physical activity
 - d. use of rescue medication
 - e. regularity of pollen sampling
 5. What are some advantages of exposure units in the evaluation of treatment for allergic rhinitis?
 - a. year-round evaluation
 - b. consistent allergen exposure
 - c. guaranteed medication compliance
 - d. complete and timely symptom assessments
 - e. all of the above
-