

The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis

Submitted to the Nonprescription Drugs Advisory Committee

**Schering-Plough Merck Pharmaceuticals
Kenilworth, NJ**

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Input is provided for the Advisory Committee based on two chamber studies conducted to examine the effects of phenylephrine on the symptoms of allergic rhinitis - especially the congestion component:

(1) One study was conducted by Schering-Plough Corporation (P04579); this compared the individual efficacies of pseudoephedrine and phenylephrine with placebo.

(2) The second study (P04822) was conducted by Schering-Plough / Merck Pharmaceuticals (SPM), a joint venture between Schering Plough and Merck. This study compared the efficacies of a novel combination product and phenylephrine with placebo.

For convenience of scientific review, these studies are being submitted together by SPM in a single submission for the December 2007 Phenylephrine Advisory Committee background package; however, the data are wholly owned by the above referenced companies.

Study P04579 was a randomized, placebo-controlled, three-way crossover study conducted at the Vienna Challenge Chamber (VCC); Prof F. Horak, Vienna, Austria, was the principal investigator. The study employed a single dose of phenylephrine 12 mg (the approved dose in the European Union), compared with pseudoephedrine 60 mg and placebo to measure nasal decongestant activity in 39 qualified subjects following exposure to grass pollen in the VCC. Phenylephrine was not significantly different from placebo in the primary endpoint, decreasing nasal congestion scores ($p=0.56$) over a 6-hour exposure. Pseudoephedrine was significantly more effective than either placebo ($p<0.01$) or phenylephrine ($p=0.01$). The results of rhinomanometry and peak inspiratory flow rate (PNIF) measurements were consistent with the conclusion based on the primary measurement. Neither phenylephrine nor pseudoephedrine had an effect on the non-nasal symptoms. There were no adverse events reported in this study.

Study P04822 was a randomized, placebo-controlled study to evaluate the efficacy of a single dose of loratadine/montelukast (L/M, 10 mg/10 mg) to placebo and phenylephrine (PE, 10 mg) in relieving nasal congestion over a 6-hour period following exposure to ragweed pollen in the Environmental Exposure Unit (EEU) in Kingston, Ontario, Canada. Prof. J. Day was the principal investigator. Qualified subjects were randomized to receive L/M, PE, or placebo when they became symptomatic following exposure to ragweed pollen in the EEU. Over the 6 hours posttreatment (primary endpoint), L/M treatment resulted in significantly greater improvement in mean nasal congestion score compared to placebo ($P=0.007$) and PE ($P<0.001$). L/M was also significantly more effective than placebo ($P=0.024$) and PE ($P=0.002$) in relieving total symptoms, nasal symptoms, non-nasal symptoms, and improving PNIF. There were no significant differences between PE and placebo for any measures. Adverse events were reported in 3.9% of the L/M subjects, 7.9% of the PE subjects and 7.1% of the placebo subjects. Most adverse events were mild or moderate in severity.

Appendix 1 contains copies of two review articles that describe allergen challenge chamber models used for the clinical evaluation of treatments for allergic rhinitis.

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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Off-label disclosure: Drs Day, Ellis, Rafeiro, Ratz, and Briscoe have indicated that this article does not include the discussion of unapproved/investigative use of a commercial product/device.

Financial disclosure: Drs Day, Ellis, Rafeiro, Ratz, and Briscoe have indicated that in the last 12 months they have not had any financial relationship, affiliation, or arrangement with any corporate sponsors or commercial entities that provide financial support, education grants, honoraria, or research support or involvement as a consultant, speaker's bureau member, or major stock shareholder whose products are prominently featured either in this article or with the groups who provide general financial support for this CME program.

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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 pathophysiological 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 terfenadine⁶¹⁻⁶³) 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 ± SD target pollen concentration of 3,500 ± 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/EAACI 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.

Credits: ACAAI designates each Annals CME Review Article for a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity. The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

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?

- traditional outpatient trial
- wheal-and-flare model
- direct nasal challenge
- outdoor (park) setting
- exposure unit

-
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
-

REVIEW

The role of allergen challenge chambers in the evaluation of anti-allergic medication: an international consensus paper

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Clinical and Experimental Allergy Reviews

Summary

Allergic rhinitis (AR) is a common condition with quality of life and economic implications for those affected. Numerous studies have attempted to evaluate treatments for rhinitis, seeking clinically meaningful efficacy and safety results to enable evidence-based treatment decisions. Traditional studies of medications for AR are hampered by many confounding environmental factors as well as suboptimal medication compliance. They are also an unsuitable setting for determination of precise pharmacodynamic properties of medications, including onset and duration of action. Allergen challenge chambers (ACCs) were developed to provide predetermined, controlled allergen levels and to limit variables inherent in traditional studies. An ACC hosts a number of allergen-sensitive subjects who may receive either medication or placebo in a closed environment regulated for temperature, humidity and other variables. Subjects' allergic responses are monitored using subjective and objective assessments throughout the study, and the resultant information contributes significantly to the clinical profile of a medication. This consensus paper provides an in-depth review of the role of ACCs as a means to evaluate treatments in AR, and concludes that ACC trials fulfil an important supportive role in the assessment of anti-allergic medication.

Keywords allergen challenge chamber, allergic rhinitis, consensus, efficacy, treatment evaluation

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Allergic rhinitis: pathophysiology and symptom management

Allergic rhinitis (AR) is an upper respiratory disorder that affects at least 20% of the population of Western countries, and its prevalence is increasing [1, 2]. The nasal mucosae and conjunctivae are mainly affected in response to normally innocuous airborne particles (allergens), being characterized by a complex of symptoms, including nasal pruritus, sneezing, rhinorrhoea and nasal congestion [3, 4], as well as ocular irritation and tearing.

Many factors affect response to allergens in susceptible individuals, including the level of allergen exposure [5, 6]. Variable exposure to allergens in different geographical

locations may contribute to the variation in prevalence of allergy internationally, or may provoke symptoms to different extents in sensitized individuals. Evidence of a positive association between atmospheric pollen counts and the prevalence of AR [7], however, has been disputed [6]. A Westernized lifestyle, including improved hygiene and the widespread use of vaccines and antibiotics, is thought to increase the likelihood of atopy [8], while climatic factors (e.g. temperature, humidity, wind currents and precipitation) are additional variables.

Although AR is not a life-threatening condition, it is associated with troublesome and at times debilitating symptoms, which can cause sleep loss, daytime somnolence, learning impairment, decreased cognitive function, decreased productivity and impaired quality of life (QoL) [9–12]. In addition, AR can be associated with comorbid

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conditions, including asthma, sinusitis, otitis media, pharyngitis, laryngitis and conjunctivitis [13]. In 1995, AR cost the US economy \$2.7 billion in direct and indirect costs [14, 15], and children lost approximately 2 million school days because of this condition [15]. It is, therefore, important that AR is managed actively and treated optimally to minimize the impact on QoL, comorbidities and costs.

Mechanism of allergic response

Individuals with a genetic predisposition for allergic reactions are described as being 'atopic'. Atopy is defined by the European Academy of Allergology and Clinical Immunology (EAACI) Task Force as 'a familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms, such as asthma, rhinoconjunctivitis or eczema/dermatitis' [16]. Symptoms are triggered by immune hyper-responsiveness to otherwise innocuous environmental stimuli (allergens), which include pollens, house dust mites (HDMs), moulds, cockroaches and animal dander. Reactivity to several allergens is common and their considerable cross-reactivity [17, 18] makes it almost impossible to eliminate exposure completely because of their widespread distribution.

Development of an allergic response involves three key stages:

- *Sensitization*: generation of allergen-specific T helper 2 (Th2) cells.
- *Early-phase*: IgE cross-linking, mast-cell degranulation and release of allergic mediators.
- *Late-phase*: sustained response because of inflammatory cell recruitment, cytokine release from Th2 cells and perpetuation of IgE production.

In susceptible individuals, initial 'sensitization' is required for an allergic reaction to develop. The reaction is mediated predominantly by IgE, leading to mast-cell activation. The degree of sensitization required differs between individuals and varies according to the size, concentration and allergenicity of the antigen; for instance, pollen grains of less than 10 µm are more allergenic than larger grains [19]. Once inhaled, the allergen is phagocytosed by antigen-presenting cells, which process the resulting peptide fragments. The epitope of the antigen is presented to major histocompatibility protein class II molecules on T lymphocytes, which leads to the generation of antigen-specific Th2 cells and B cells.

The early phase of the allergic reaction is typified by elevated levels of IgE. IgE binds to its high-affinity receptor (FcεRI) on mast cells and other effector cells, which, in a sensitized individual, leads to cross-linking of IgE-FcεRI complexes. This results in mast-cell degranula-

tion with the release of histamine, leukotrienes, chemokines and cytokines, such as interleukin (IL)-4, IL-5 and IL-6, tumour necrosis factor-α and granulocyte-macrophage colony-stimulating factor. A sustained inflammation follows, known as the late-phase response. This is maintained by Th2 cells and other inflammatory cells, such as eosinophils and basophils, which enhance IgE production.

Clinical presentation of allergic rhinitis

Symptom patterns – severity and duration. Mast-cell degranulation results in rhinorrhoea, sneezing, nasal obstruction and nasal and conjunctival itching – the classic symptoms of AR. Traditionally, AR has been subcategorized based on whether these symptoms are experienced for part of the year or all year round as follows:

- *Seasonal AR (SAR)*: triggered by pollens and/or moulds that are only present for certain months of the year.
- *Perennial AR (PAR)*: triggered by HDMs, indoor moulds, cockroaches or animal dander, all of which may be present year round.

In 2001, the World Health Organization (WHO) published guidelines on Allergic Rhinitis and its Impact on Asthma (ARIA), and proposed a new disease classification on which to base rhinitis treatment [20]. This model categorizes rhinitis according to persistence and severity of symptoms, with severity criteria based on the impact that symptoms have on QoL (Table 1).

Priming. The priming effect has been defined as an increase in reactivity of the nasal membrane following repeated exposure to pollen [21]. The application of this effect in an allergen challenge chamber (ACC) environment is to increase the level of sensitivity to a specific

Table 1. Classification of allergic rhinitis, based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [20]

Classification	Symptoms
Intermittent	≤ 4 days/week or ≤ 4 weeks/year
Persistent	> 4 days/week and > 4 weeks/year
Mild	All of the following: Normal sleep No impairment of daily activities Normal work No troublesome symptoms
Moderate-to-severe	One or more of the following: Abnormal sleep Impairment of daily activities Abnormal work Troublesome symptoms

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Table 2. Rhinitis treatments and their main targets

Class	Example agents	Target	Mechanism
Antihistamines	Desloratadine Fexofenadine Levocetirizine	H1 receptors	Antagonism of H1 receptor, preventing activation of H1 receptor-containing cells Receptor-independent anti-inflammatory effects [144]
Leukotriene modifiers	Montelukast Zafirlukast	Leukotriene receptors	Competitive blockade of leukotriene receptors Additive effects with antihistamines
Corticosteroids	Beclomethasone Mometasone	Chemokines	Inhibition of IL-1, TNF and prostaglandin synthesis Other anti-inflammatory effects Immunosuppressive
Cromolyns	Nedocromil	Mast cells	Inhibition of histamine release, mast-cell stabilization
IgE antibodies	Omalizumab	IgE	Prevention of IgE binding to mast cells

IgE, immunoglobulin E; IL, interleukin; TNF, tumour necrosis factor.

allergen (e.g. ragweed or grass pollens), mimicking the natural process and facilitating the development of adequate symptoms for subject participation. A mucosal response to one allergen has been found to lead to increased sensitivity (or reduced symptom threshold) to other allergens, related to a variety of factors arising from earlier exposures [5, 22, 23]. Factors affecting the rate and degree of symptom development during the priming process are under study [24]. The Environmental Exposure Unit (EEU) in Kingston uses the priming effect by exposing subjects to ragweed pollen for one or more times in the 2 weeks prior to the study date.

Priming, both inside and outside of an ACC environment, usually develops early and may be ongoing, depending in part on current allergen exposure. For instance, it has been reported that at the beginning of the season, 90% of people with sensitization to *Betula* pollen develop symptoms with pollen counts higher than 80 grains/m³, but by the end of the season, counts that induce symptoms decrease to 30 grains/m³ [5]. Furthermore, this may be exacerbated by the presence of *Alnus* and *Corylus* pollens, with which *Betula* shares antigens [5]. This heightened sensitivity may also make an affected individual sensitive to other triggers or to irritants, such as tobacco smoke, which may not normally have caused a reaction [15].

Management of allergic rhinitis

Allergen avoidance. Most guidelines for AR suggest that allergen avoidance techniques should be an integral part of a management strategy [20]. It should be attempted in order to mitigate symptom severity [25]; but allergen avoidance has had limited success, in particular, because of widespread distribution of seasonal allergens [26, 27]. Therefore, management of AR usually includes therapeutic intervention.

Medications. Currently, there are five classes of drug treatments for AR (Table 2), each of which targets a

different stage of the allergic reaction. These therapies may behave synergistically when used in combination, allowing better control of symptoms [28].

Histamine, released from the cytoplasmic granules of basophils and mast cells, plays a major role in AR. Antihistamines are currently the mainstay of AR treatment because of their effectiveness in controlling symptoms [14, 29]. They are competitive, reversible antagonists of histamine at H1-receptor sites on nasal mucosae, but they do not prevent histamine release or bind to histamine that has been released already. Antihistamines effectively alleviate symptoms attributed to the early-phase reaction, such as rhinorrhoea, pruritus and sneezing [29]. They also affect the late-phase reaction by reducing eosinophil infiltration and adhesion molecule expression [30].

Intranasal corticosteroids have a longer onset of action than antihistamines; although they are intended to be taken regularly, rather than as needed (PRN) [29], recent evidence of earlier onset indicates a possible PRN role in certain situations [31]. Intranasal corticosteroids, which have been found to be effective at controlling chronic inflammation are the first choice in the treatment of moderate-to-severe symptoms, and may be used concomitantly with oral antihistamines [20].

Cromolyns, administered intranasally, are sometimes used for mild, persistent disease, but are less effective than antihistamines or corticosteroids [29]. Leukotriene modifiers are indicated for the treatment of asthma and represent a useful approach to the treatment of AR, especially when used in combination with other treatments [32].

Owing to the range of treatments available, it is important that physicians have adequate information regarding the different properties of each drug so that they can prescribe the most appropriate agent for their patients. Medications should have a rapid onset of action, which is considered to be the most desirable property when selecting a treatment for rhinitis [33], as most

patients do not use medications regularly, even when they are prescribed for daily use [34].

An ideal AR treatment would:

- be effective in most subjects;
- provide fast symptom relief;
- prevent development of chronic inflammation or manage it if it begins;
- maintain activity over the full 24 h period between doses;
- require no co-medications;
- be effective against all individual rhinitis symptoms;
- have a good safety profile, conducive to long-term use;
- also be effective for non-rhinitis symptoms;
- improve QoL.

Immunotherapy. Allergen immunotherapy, in the form of repeated oral, sublingual, intranasal or subcutaneous administration of standardized allergen extracts, has been shown to be effective in reducing the intensity of symptoms and need for medications, as well as improving QoL [20, 35, 36]. A recent meta-analysis has confirmed the efficacy of sublingual immunotherapy (SLIT) [37], and double-blind, placebo-controlled trials have shown subcutaneous and SLIT to be comparable and significantly better than placebo for treatment of AR [38].

Subcutaneous injections carry the risk of local reactions at the injection site or more serious systemic reactions, such as anaphylaxis [39]. Postmarketing surveillance studies, however, have indicated a more favourable safety profile for SLIT [20], even in paediatric populations [40, 41]. Studies have indicated that SLIT can modify the course of the disease [35], restricting development of asthma in subjects with AR [42, 43]. However, the long-term efficacy of SLIT needs to be evaluated further. As such, immunotherapy should not be considered an ultimate treatment of respiratory allergy, but a therapeutic tool to be harmonized with pharmacological treatments [20].

Allergy research techniques

Traditional SAR trials are performed during the pollen season for up to several weeks. However, a number of variables, including differences in pollen levels over the course of the study, subject compliance and recall bias, reduce their sensitivity. When trials are conducted in multiple locations, some of these variations (such as pollen levels) may be exaggerated and are harder to adjust for. In addition, because study participants are not monitored, traditional trials are not suitable for the determination of consistent, frequent, precisely timed symptom assessments [44]. These factors contribute to a traditional trial's insensitivity for detecting onset and duration of action differences between treatments, or differences between various doses of the same treatment. This may

be one explanation as to why onset of action is an endpoint that would be difficult to monitor in traditional studies and why it is rarely measured.

The essential factor in establishing drug efficacy in AR is the ability to differentiate placebo from treatment effect. Of importance, but difficult to establish, are clinically meaningful differences between active treatment arms. In order to prescribe the most effective agent for each patient, physicians need to be able to characterize important differences between treatments.

Randomized, controlled trials (RCTs) are accepted as the standard method of assessment of treatment efficacy and safety, and a well-designed RCT for AR interventions should:

- control allergenic stimuli and alleviate variations in exposure;
- select subjects sensitive to a common allergen, with a spectrum of response;
- rigorously evaluate symptoms in response to treatment;
- search for and identify adverse events;
- be clinically relevant to 'real life'.

Assessing clinical outcomes

Subjective evaluation. Subject self-reporting of response is central to the investigation of AR treatments. Trial participants are asked to evaluate the frequency and severity of their symptoms, using, for example, a verbal scale (Table 3), visual analogue scale (VAS) [45] or graphical scale.

Although symptom scores are subjective, they provide a measure of the effect of an allergen in an individual and give the investigator the ability to look at change in individual symptoms over time. In addition to nasal symptoms, ocular symptoms of AR can be assessed by the extent of conjunctival itching, redness and tearing. Individual symptoms can also be grouped to give an overall score, for example the major symptom complex (MSC) or the total symptom complex (TSC) scores (Table 4) [46, 47].

Objective evaluation. Objective evaluation of respiratory parameters supports subjects' subjective rating of symptom severity and treatment response. Techniques include rhinomanometry, weighing of nasal secretions in paper

Table 3. Example of a 4-point verbal scale for measurement of allergic rhinitis symptoms

Score	Symptoms
0 = None	No symptom(s) evident
1 = Mild	Symptom(s) present but easily tolerated
2 = Moderate	Definite awareness of symptom(s); bothersome but tolerable
3 = Severe	Symptom(s) hard to tolerate; interfere(s) with daily activities

tissues, nasal peak inspiratory and expiratory flow, nasal endoscopy, nasal lavage and spirometry (Table 5). More than one measurement may be used: for example, the sneeze count and the weight of nasal secretions can be combined as a 'sneeze-drip' score. Beyond respiratory assessments, digital imaging can be used to evaluate the conjunctival vascular reaction [51], and serum levels of proinflammatory mediators can also be monitored.

Quality of life and global evaluation. The impact of AR on QoL is considerable, and it is important to include this in the medication assessment [52]. QoL questionnaires can

be used to measure not only the symptom relief associated with a given treatment, but also the effect on subjects' lives. Furthermore, poor QoL at study baseline may contribute to the placebo effect that is often seen in rhinitis trials [53], and the use of such questionnaires may help to ascertain this.

Generic and disease-specific questionnaires can be used, and accepted questionnaires include the Medical Outcomes Study 36-Item Short Form (SF-36) Health Status Questionnaire [54] or the Rhinitis Quality of Life Questionnaire (RQLQ) [55]. Use of these surveys allows the effects of rhinitis on QoL to be acknowledged, which may otherwise be ignored or trivialized [15].

Table 4. Example of two multisymptom scores for assessment of allergic rhinitis [46, 47]

MSC score*	TSC score
Runny nose	MSC
Sniffles	Itchy eyes and ears
Itchy nose	Itchy throat
Watery eyes	Cough
Sneezes	Postnasal drip
Nose blows	

*Symptoms rated on a 5-point scale, except for sneezes and nose blows (8-point scale).

MSC, major symptom complex; TSC, total symptom complex.

Allergen provocation tests and clinical trial settings

A number of models have been used to conduct RCTs to evaluate medications for AR. These models will be reviewed briefly.

Histamine/allergen provocation tests. Provocation tests using histamine or specific antigens are important models, not only for identifying causative allergens, but also for evaluating and comparing new therapeutic agents. As such, they are often used as a preliminary evaluation tool for medications for AR [56].

Table 5. Techniques for obtaining objective data on allergic rhinitis

Technique	Data obtained
Weal and flare skin challenge	Although not a true respiratory parameter, this allows pharmacological data between drugs to be assessed and compared using the skin response to applied histamine and/or allergen
Rhinomanometry	Sensitive assessment of nasal obstruction (nasal airflow, resistance and airflow increase) by measuring the difference between prenasal and postnasal pressure and the corresponding nasal flow
Acoustic rhinometry	Audible sounds (150–10 000 Hz) that are propagated in a tube are affected by nasal impedance, helping to define structural and mucosal components of the nasal passage
Rhinostereometry	Nasal mucosae are observed through a surgical microscope to detect changes in mucosal swelling
Nasal endoscopy	Provides an endoscopic image of the nasal cavity, which can be recorded as digital images or video for comparison with subsequent investigations. To calculate nasal patency and severity of turbinate swelling, the images are rated according to a 5-point scale (0 = nasal airways completely open; 4 = nasal airways completely obstructed). The sum of scores from both nostrils indicates the clinical significance of symptoms
Nasal peak inspiratory and expiratory flow	Simple method of assessing nasal obstruction, the maximal inspiratory and expiratory nasal airflow volumes being expressed in L/min
Nasal secretion	Nasal secretions can be collected in a sealed container or on tissues, either of which are weighed before and after use to estimate the severity of nasal secretion
Nasal lavage	Nasal micro-lavage can be performed during and after allergen exposure. Allergic mediators such as histamine, prostaglandins and leukotrienes can then be quantified [48–50]. Nasal levels of ECP can also be measured
Spirometry	Forced expiratory volume in 1 s (FEV ₁) is monitored at baseline and during allergen exposure
Conjunctival digital imaging	Selected areas (2.3–3.5 mm) of the conjunctivae are documented by digital imaging during allergen challenge sessions to assess changes in conjunctival vascular reaction [51]
Ocular hyperaemia and oedema	Examined using a slit lamp to support conjunctival digital imaging results
Serum ECP	Serum levels of ECP are higher in subjects with an inflammatory allergic response than in non-atopic individuals
Exhaled and nasal nitric oxide	Levels of exhaled and nasal nitric oxide are elevated in individuals with allergic bronchial and nasal inflammation

ECP, eosinophil cationic protein.

Skin prick tests. Skin prick challenge is a simple method, with both allergen and histamine being easy to apply. Skin provocation with histamine is one of the methods used most commonly for preliminary evaluation of medications for AR [57]. It is also a cheap, rapid and accurate method of identifying allergen sensitivity, whereby mast-cell activation in the skin causes a characteristic 'weal and flare' reaction in response to allergen administration. The skin prick test is often a precursor to nasal allergen provocation tests. Data show a correlation between skin and upper respiratory effects of antihistamines [58], and there is a long-standing tradition of extrapolating data from the skin to the airways in clinical practice. However, the use of data from these studies may not be predictive of the clinical efficacy of antihistamines for rhinitis symptoms and has been challenged [59].

Ocular provocation test. The standard ocular (or conjunctival) provocation test begins with a titration of the selected allergen applied to both eyes of each subject. This enables gradation of symptoms using standardized scales. The quantity of allergen applied is increased up to a predetermined threshold of response, which enables a difference to be seen between drug and placebo responses. In subsequent sessions, placebo solution is applied to one eye and the study drug to the other, before challenge with allergen in both eyes. The eyes can then be monitored for symptoms of allergy, and the responses compared [51, 60].

This method enables determination of the onset and duration of action of treatments. By enrolling subjects based on their initial response to allergen, only individuals with sufficient responses are included, and the titration provides a mechanism to ensure sufficient reactivity. One advantage of this method for evaluating the pharmacodynamics of a treatment is that the other eye can serve as an easily accessible control [61]. However, as the allergen concentration applied is usually higher than environmental levels, this must be accounted for when determining clinical relevance. Furthermore, information obtained from an ocular challenge cannot be extrapolated directly to the respiratory system. Therefore, in AR research, this method offers supporting data only.

Nasal provocation test. Nasal provocation tests (NPTs) to histamine or suspected allergens provide meaningful results, and a correlation between skin tests and NPTs has been reported [62]. NPTs are now recognized by the international Global Resources In Allergy (GLORIA™) [63] as an additional resource for the diagnosis of AR.

There are a number of techniques for the application of allergen to the nasal mucosae, including delivery of allergen in powdered form, via sprays or nebulizers, from a syringe, topically using cotton wool or by impregnation onto paper discs. Response to nasal provocation can be assessed both

subjectively and objectively by a variety of methods, as listed in Table 5. An advantage of the nasal provocation test is the potential for critical evaluation of the kinetic response to stimuli, rechallenge and treatment [23].

Traditional outpatient studies. Traditional outpatient trials for AR are randomized and double blinded to compare the drug of interest with placebo and one or more active agents over a period of usually 2 or more weeks while study participants carry on with their normal daily activities. SAR trials are undertaken during the pollen season and are therefore restricted in timing and duration. PAR trials are conducted out of the allergy season to avoid the confounding effects of pollen exposure. Subjects are given diaries to complete at home for the duration of the study to record symptoms of rhinitis and satisfaction with treatment over 12 or 24 h intervals. This reflective scoring provides an estimate of the overall effectiveness of the treatment over the observed time period. In addition, an end-of-dosing-interval score can be recorded to evaluate the duration of effect. Diurnal variations, commonly seen in subjects with AR, can also be monitored.

Parallel-group trials compare placebo with one or more active treatment arms, with each randomized group receiving a different study treatment. These are usually multi-centre studies, as they require large numbers of subjects per group to achieve sufficient statistical power to see even small differences between the study arms. A crossover design may be used in PAR trials where a single group of subjects successively receives each of the study medications, and each treatment course is separated by a wash-out period. This methodology requires fewer subjects than the parallel-group design, but assumes that AR is stable within one individual over time, and that the selected washout period eliminates the carry-over effect between treatments. Crossover designs are logistically difficult to carry out in traditional SAR trials, mainly because of the short duration of the pollen season in many places [64] and the priming effect [21].

The traditional outpatient trial is the most commonly used method for the investigation of medications for AR. It is the best characterized approach and is recognized as such by regulatory authorities, who provide guidelines on methodology and interpretation of results of clinical trials. It is the only study system to date that is fully accepted as representing a 'real life' setting.

However, there are a number of limitations to traditional outpatient trials. Although widely considered to reflect 'real life', they rely on a number of assumptions and are unable to account for the high number of uncontrolled variables, making them relatively insensitive for the determination of subtle differences between treatment arms.

Notably, there are large variations in the timing of the pollen seasons and in diurnal and annual pollen counts.

Growth conditions, altitude [65] and meteorological factors such as wind or rainfall continually influence concentrations of pollen in the atmosphere [66, 67], producing considerable variation in and between seasons [68]. However, regional pollen counts do not necessarily represent the levels experienced by any one individual, as work and recreational factors contribute to the level of personal pollen exposure. Thus, wide differences in subject exposure occur, giving variable baseline symptom levels that are hard to correct for in subsequent analyses. Additionally, variations in pollen levels from location to location probably contribute to differences in results obtained at different sites in multicentre studies. These factors, as well as variations in pollen levels from year to year, make it almost impossible to reproduce trial conditions and results. A significant placebo effect is often observed in such study settings, which may be because pollen exposure is insufficient to induce symptoms throughout the study, misleadingly implying a protective or treatment effect, especially later in the trials when interpretation of medication effect would coincide with the normal decline in seasonal pollen levels [69].

In addition to the variability of pollen exposure, subject compliance with study procedures such as the acknowledged last-minute completion or backdating of symptom assessments also contributes to reduced sensitivity in the data from traditional trials. It is also difficult to accurately assess compliance with trial medications, and whether other medications or interventions that might affect response to the study medication have been taken.

The dropout rate in outpatient trials is often high, meaning that a number of study centres are needed to ensure sufficient subject numbers to obtain statistical power. Thus, despite following the same protocol, the heterogeneous population and study conditions used increase the likelihood of a spread of results, often leading to significant differences in the results from different trial centres.

Investigators, in response to the variables associated with traditional clinical trials, have developed alternative strategies such as day-in-the-park studies and ACCs to limit some of these variables and to better define performance of anti-allergic medications [44].

Day-in-the-park studies. When outpatient trials are conducted at multiple centres and subjects follow their usual lifestyle for the duration of the study, there is a wide variation in the frequency, duration and intensity of allergen exposure among the participants. Day-in-the-park studies, first conducted in the late 1970s [70], attempt to limit this variation in exposure by conducting SAR studies outdoors, over 1–2 days. By selecting a park location, the objective is to assure pollen exposure and limit other variables. Numerous park studies have been published [71–78].

Trials are conducted during the pollen season – ideally when allergen levels are at a peak – and are randomized, double-blind, parallel-group designs. A large number of potential subjects are screened for sensitivity to the prevalent pollen and other inclusion/exclusion criteria, and qualifying subjects are asked to attend the treatment day at a prearranged site. Subjects are exposed to ambient allergens in the park setting and asked to rate their symptoms on diary cards. If they attain symptoms of a sufficient level, they are given a medication and remain at the trial site, under observation by the investigators [72]. This ensures that subjects are exposed to similar environmental conditions, receive treatment at the same time and report symptoms regularly, thus avoiding missing data. Subject activities, including physical activity and food intake (e.g. citrus), are also monitored, and variables such as medication compliance are recorded. Subject compliance with procedures, including completion of diary cards, is easier to control and, because of the short duration of trials, continuous attendance of subjects is improved and monitoring by staff throughout the trial is possible.

This method provides pharmacodynamic data such as onset and duration of action, but because of the usual short-term nature of these studies, there may be limited information on safety. However, there are practical difficulties in setting up day-in-the-park trials, as the pollen season is limited and there is the risk of disruption by adverse weather conditions. Furthermore, the peak of the pollen season can only be estimated and thus maximal allergen exposure is not assured [44]. Intra-individual allergen exposure is difficult to determine and is not standardized during the trial period. Pollen levels are not always recorded and publications often lack supporting evidence as to their relationship with the seasonal peaks in pollen levels [44]. Variable pollen levels within and between seasons remain confounding variables that make repetition of results difficult.

Allergen challenge chamber studies. An ACC is a specially designed room that hosts study participants in a controlled environment, in which AR symptoms, treatment effect and differences between treatments are assessed in response to ambient allergen. The development of ACCs began in the 1980s [79], with the first clinical trial published in 1988 [80]. The technique is based on the concept that uniform exposure to controlled levels of allergen enables an accurate analysis of treatment efficacy without the variables inherent in traditional studies. The ACC has been recognized as being at least equivalent to histamine or allergen provocation models, with established reproducibility of results [81–83].

The air within an ACC is filtered to remove extraneous allergens and pollutants (Fig. 1), and is strictly controlled and adjusted for allergen type and concentration,

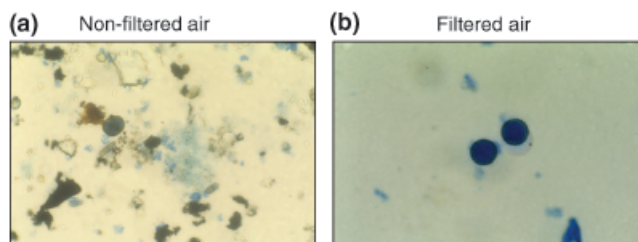


Fig. 1. Micrographs of air samples from (a) non-filtered and (b) filtered air in the Kingston Environmental Exposure Unit. Supplied courtesy of J. Day.

temperature, humidity, CO₂ concentration and airflow. Allergen concentration is the most important constant in this system – a well-documented, uniform concentration of allergen must be achieved throughout the exposure area of the chamber, and the concentration is carefully selected to be relevant to levels found outdoors. The aim is for all subjects to be exposed to the same predetermined concentration of allergen, regardless of their location within the chamber or the time of their participation, as measured by regular sampling during the study period. The resulting conditions enable highly reproducible results that are consistent throughout each study.

Conventional nasal or conjunctival challenge tests may induce a response in normally asymptomatic subjects because of the tendency to administer high allergen concentrations in the absence of a predefined ‘maximum dose’ [84]. Levels of allergen in an ACC (i.e. peak seasonal) induce responses in only those subjects who would generate a response in ‘real life’ [85]. Furthermore, non-allergic staff members do not report symptoms, despite repeated pollen exposures over a number of years in ACC settings.

Studies conducted in ACCs to date have been monocentric, with the lead investigator ensuring consistency of conditions in each session throughout the study [46, 47, 86, 87]. Parallel-group or crossover designs can be used, with single or multiple medication intakes and with single or multiple allergen types. SAR studies may be conducted both in and out of the pollen season in an ACC. In-season studies allow control of many factors that cannot be regulated in traditional trial methodologies. Additionally, there is less priming required compared with out-of-season studies, especially for subjects who are already symptomatic (primed). The capability of conducting studies year round also offers scheduling advantages independent of pollen exposure conditions.

In the EEU, subjects are exposed to a predetermined concentration of allergen during the priming phase. Participants who attain sufficient allergic symptoms can then be randomized to participate in the treatment phase, where they are exposed to the single test allergen at concentrations at which they have demonstrated sensitiv-

ity during priming. As other parameters are controlled, differences in response observed between treatment groups should be because of differences in drug activity.

Both subjective and objective data are retrieved, with data being immediately available. Participants take medications at a precise time(s) and complete symptom diaries at specified intervals under constant observation by study personnel. Thus, timely symptom assessments and medication compliance can be ensured. This helps to avoid the typical problems in outpatient trials of non-compliance, missing data or inaccurate ‘last-minute’ diary completion, and makes the ACC especially suitable for assessing precisely timed efficacy measures such as onset of action.

ACCs can overcome many of the problems associated with traditional trials. As an ACC permits large amounts of precise numerical data to be gathered, statistically significant results can be obtained with far fewer subjects than would be needed in an outpatient trial. This also has ethical considerations, as fewer subjects are exposed to investigational agents or placebo. Subjective data can be supplemented with periodic objective measurements, such as nasal inspiratory flow rate [31], lung function [88] or conjunctival vascular reaction [51]. Additionally, nasal secretions can be used to measure the release of allergic mediators and cytokines at any point [50].

Challenge chambers permit assessment of the relative efficacy of anti-allergic medications and also allow the possibility of exploring the dynamics of allergic symptoms and their impact on cognitive function. ACCs provide a uniquely cost-effective setting for bioequivalence studies of both topical nasal products and eye preparations, and they are an ideal method for proof-of-concept studies for agents in early Phase II development. At this stage of drug development, the results obtained in animal studies can be confirmed or rejected in humans, and ACC studies can establish this within a short timeframe, with evident advantages.

ACCs allow precisely timed measures of efficacy at regular intervals, and data on onset and duration of action can be obtained more accurately than with traditional trials. The rapid alleviation of symptoms is one of the most important factors for a subject, ensuring treatment compliance, satisfaction and overall QoL. In recognition of this, onset and duration of action have been recommended by the ARIA/EAACI workshop group as important pharmacodynamic characteristics of anti-allergic medications, to facilitate once-daily administration of treatments and clinical efficacy at the end of each dosing period [89].

QoL has been evaluated in ACC trials, both to examine the impact of studies where subjects’ allergic symptoms are induced as part of the study design [90] and to determine if there is a relationship between QoL score and the likelihood that a study participant would respond to placebo [53]. A QoL questionnaire expressly designed for ACC trials is in the process of being validated. ‘Real

life' pathophysiological mechanisms such as diurnal variability, or long-term endpoints such as pharmacoeconomics, have not yet been explored.

Guidelines on conducting allergic rhinitis trials

Difficulties in conducting rhinitis trials

The Food and Drug Administration (FDA) (FDA guidance remains draft and not for implementation) and European Medicines Agency (EMA) have both issued guidance/guidelines on the clinical development of medications for the treatment of AR, and both acknowledge the difficulties that exist in conducting meaningful trials on this subject [3, 4]. Key issues include the following:

- the likelihood that subjects will have multiple allergic triggers or comorbidities with overlapping symptoms, such as sinusitis, allergic conjunctivitis or asthma [3, 4];
- recruitment of subjects who turn out to be asymptomatic or have only mild rhinitis symptoms at baseline [3, 4];
- the subjective nature of subjects' symptom assessments and self-reporting of compliance [3];
- inter- and intra-individual variability in allergen exposure during the study [3, 4];
- the difficulty in estimating the peak of the pollen season [3];
- spontaneous variability of severity and nature of symptoms within an individual [4];
- the wide variety of study designs, with different endpoints, durations and data analysis techniques [4];
- the need to consider multiplicity (multiple possible rhinitis symptoms, numerous repeated measures in individuals) and a possible need to make *post hoc* changes to the protocol or analysis (e.g. redefinition of primary efficacy, change in the analysis set or redefinition of the pollen season) [4].

Food and Drug Administration and European Medicines Agency recommendations for research

Both the FDA guidance and EMA guidelines note that studies during the developmental programme for a new anti-rhinitis drug often fail to demonstrate the effectiveness of the treatment [3, 4]. Each recommends at least two adequate and well-controlled Phase III trials for approval of a SAR or PAR indication for a new product [3, 4]. The dose-response relationship must be evaluated using either clinical (traditional outpatient trials) or validated pharmacodynamic studies [4]. Randomization, placebo control and an active control arm are all required to account for the variable nature of the disease and the subjectivity of data collected [3, 4]. Studies should be double-blind, parallel-group designs, ideally with a placebo run-in period [3]. Non-inferiority trials are not possible because

of lack of sensitivity, and superiority trials should be conducted against a well-established comparator with the same route of administration [4]. Non-inferiority cannot be claimed from superiority trials in the absence of a placebo arm for internal validation [4].

Pollen counts should be measured at the different study centres, to document the exposure of subjects to relevant allergens during the study period [3, 4]. However, personal exposure is dependent not only on weather but also on individual factors such as frequency and duration of outdoor exposure. Personal monitoring of exposure, although possible, is technically complicated and not feasible in large-scale trials [64]. Randomization of subjects in each centre should be conducted over a short time period to reduce variability in allergen exposure, and PAR trials should be conducted out of the pollen season [3]. The FDA guidance states that the duration of a double-blind period should be at least 2 weeks for SAR and 4 weeks for PAR [3]. The EMA guidelines note that the study duration may vary depending on the onset of action of the product, indication sought (treatment vs. prevention of symptoms) and duration of allergen exposure expected [4]. In traditional clinical studies, the EMA-recommended duration for the double-blind period of SAR trials is 2–4 weeks, and 6–12 weeks for PAR trials [4].

Safety is of the utmost importance for AR treatments – products are likely to be used over the long term, and although rhinitis may be chronic and disabling, it is not life threatening. Thus, safety data from long-term exposure for up to 12 months in at least 100 subjects [91] should be available. Subjects with comorbid conditions may be included in trials for the purposes of safety analyses only [4].

Subjects with asthma require special consideration, as asthma and AR commonly occur together. Subjects with mild intermittent asthma are included routinely in trials, although those with at least moderate asthma triggered by the study allergen are usually excluded to avoid exacerbation of symptoms. The FDA states that subjects with asthma, with the exception of mild, intermittent asthma, should be excluded [3], while the EMA allows inclusion of asthmatic subjects for the purpose of obtaining safety data [4].

Even though regulatory authorities acknowledge the use of the ACC setting, referred to as an environmental exposure unit in their guidelines/guidance, the EMA requires that justification is provided for its use and validity, and both the FDA and the EMA restrict this to a limited role and provide no guidance on how to assess the results [3, 4]. Neither is any guidance given for how to interpret day-in-the-park studies. Formalization and standardization of trial methodology and analysis would allow more homogeneous data sets to be collected, enabling better comparisons between different trial types.

Allergen challenge chambers: Food and Drug Administration guidance

Three settings are recommended by FDA guidance to study the onset of action of agents, one of which is the ACC [3]. Results from the ACC, as well as those derived in the park setting, must be replicated if they are used to support an onset of action claim that is shorter than that observed in Phase III trials (i.e. a traditional outpatient study), despite both models being acknowledged as settings for assessing onset of action [3]. This is because of the shorter duration of these studies, the restricted setting and the manner in which they are conducted. The use of an ACC in SAR prophylaxis trials is also recommended [3].

Allergen challenge chambers: European Medicines Agency guidelines

The ACC model is included within current EMEA rhinoconjunctivitis drug development guidelines as a possible pharmacodynamic assessment tool, to provide supportive evidence of superiority over placebo and to compare local vs. systemic therapy for AR and conjunctivitis [4]. The EMEA also lists validated pharmacodynamic studies as an alternative to clinical studies for establishing the effective dose range and optimal dose of a treatment, provided the route of allergen challenge is made in line with the intended indication. However, the ACC is currently grouped in the same investigative category as the nasal allergen challenge and conjunctival allergen challenge, and is not yet recognized by the EMEA as a valid, stand-alone method for therapeutic efficacy.

Allergen challenge chambers

Physical set-up

The number of ACCs available worldwide is limited because of the complexity of the physical set-up required to ensure a controlled density of particles. However, several ACCs exist, with more under development. In the order of longest standing, the chambers commonly used in allergy RCTs are:

- the Vienna Challenge Chamber (VCC) at the University Clinic, General Hospital, Vienna, Austria;
- the VCC at the Allergy Centre, Vienna West, Austria;
- the EEU at Kingston General Hospital, Ontario, Canada;
- the Chamber at National University Hospital, Copenhagen, Denmark;
- the Allergen Exposure Unit (AEU) in Atlanta, Georgia, USA;
- the Environmental Exposure Chamber (EEC) at Allied Research International, Mississauga, Ontario, Canada;
- the ACC at Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany;
- the EEU Wakayama, Wakayama, Japan;
- the ACC at Osaka Medical University, Osaka, Japan. (Although the EEC, the EEU Wakayama and the Osaka ACC have been identified as allergen challenge chambers, studies utilizing these units have not been published in peer-reviewed journals to date.)

The individual chambers possess some physical and technical differences (Table 6), but the characteristics are the same:

- studies are not limited to the period of natural pollination;
- controlled and uniform allergen exposure;
- no impact of weather conditions;
- no impact of personal context (participation in outdoor activities, etc.);
- ensured compliance (medication administration, timeliness and completion of symptom assessments);
- instantaneous and precisely timed symptom assessments.

As experience with ACC studies has been acquired mostly from the VCC (Vienna, Austria) and the EEU (Kingston, Canada), these allergen challenge systems will comprise the focus of discussion in subsequent sections.

Vienna Challenge Chamber, University Clinic of Vienna. The longest-standing allergen challenge system, the VCC, first discussed in the literature in 1987 [79], is situated in the University Clinic of Vienna, Austria. It was developed in 1985 and extensively rebuilt in the new building of the University Hospital in 1992. It is an enclosed system where up to 14 participants enter through an airlock and are challenged simultaneously, usually for between 2 and 8 h. The key features of the VCC are outlined in Table 7 and Fig. 2.

Environmental Exposure Unit, Kingston General Hospital. The EEU was first developed in 1981 as a system for testing the respiratory effects of urea formaldehyde foam insulation [96]. In 1987 it was permanently modified for allergen challenge. The system circulates fresh, filtered outdoor air and room air exits through ceiling vents. Pollen is dispersed into the airflow and propelled around the room by fans. Frequent sampling throughout the seating area gives an accurate measurement of allergen concentration during the study, and allergen levels are replenished to maintain a constant level during the challenge session [92].

The key features and physical set-up of the EEU are shown in Table 8 and Figs 3 and 4.

A controlled environment

The ACC has proved effective in multiple studies evaluating various aspects of AR. It has been used to investigate the priming effect of ragweed pollen, the onset of allergic

Table 6. Published, peer-reviewed accounts of the physical features and capacity of existing allergen challenge chambers

	Vienna: University Clinic VCC [79, 87, 93]	Kingston: EEU [92]	Vienna: Allergy Center [93]	Copenhagen [94]	Atlanta [95]	Hannover [88]
Size	Area: 13.78 m ² Height: 2.7 m	Area: 303 m ² Height: 2.74 m	Area: 21 m ² Height: 2.8 m	Area: 5 m ² Maximum height: 2.6 m	Area: 360 m ² Height: 3.6 m	Area: 47 m ² Height: 2.8 m
Capacity (number of subjects)	Specially constructed room, hosting up to 14	Modified room in a hospital setting, seating up to 160	Specially adapted room, hosting up to 24	Portable tent designed to be adaptable to an existing room, hosting a single occupant	Specially constructed room, seating up to 150	Specially adapted room, seating up to 18 (up to 25 in subsequent studies)
Ventilation/dispersion system	Air enters through openings in the ceiling, and used air is sucked out through openings at floor level Second air circuit for allergen-loaded air delivered from the ceiling	100% outdoor air, filtered through Farr 30/30 and Farr Riga-Flo 200 filters Airflow of 3200 cfm Pollen feeder emits pollen into the unit	Filtered air, completely conditioned Second air circuit for allergen-loaded air	Inlet vent and micropore filter Allergen administered as aerosol through nebulizer connected to inlet pipe Air volume flow range 4000–6000 L/h	Outdoor air ventilation at rate of ≥ 5 cfm/person HVAC supply airflow rate of ~1.67 cfm/square foot	Filtered air (HEPA) with push-pull ventilation system Air is mixed by 14 swirl inlets for incoming air and thermal convection from floor heating
Typical allergen load	1500 grass pollen grains/m ³ (700–2000 grains/m ³) 20–110 ng/m ³ <i>Der p 1</i>	3500 ± 500 ragweed pollen grains/m ³	1400 grass pollen grains/m ³ 90 ng/m ³ <i>Der p 1</i>	Theoretical maximum of 50–100 ng/m ³ <i>Der p 1</i>	3000–4500 ragweed pollen grains/m ³	1000–8000 grass pollen grains/m ³
Allergen load monitoring	Modified Burkard pollen traps make measurements every 5 min	Pollen counts collected by seven Rotorod samplers, every 30 min	Every 5 min	Portable air sampling unit Outlet air sampler	Pollen counts collected by five Rotorod samplers, every 30 min	Pollen concentration monitored every minute by a laser particle counter and every 30 min by two Rotorod samplers

cfm, ft³/min; *Der p 1*, *Dermatophagoides pteronyssinus*; EEU, environmental exposure unit; HEPA, high efficiency particulate air; HVAC, heating-ventilation air-conditioning; VCC, Vienna challenge chamber.

Table 7. Key features of the University Clinic Vienna Challenge Chamber (VCC)

Feature	Specification
Chamber	Length: 5.25 m; width: 2.60 m; height: 2.70 m Area: 13.78 m ² Volume: 37.20 m ³ Materials: Smooth aluminium surfaces to reduce allergen adherence (also antistatic measures and thorough cleaning between challenge sessions)
Airlock	Area: 1.30 m ²
Working space	Area: 42.50 m ² Windows between chamber and working space allow constant observation of subjects
Number of participants	Up to 14
Ventilation system	Indoor air ventilation system, blowing fresh air into the chamber through openings in the ceiling, and sucking out used air through six openings close to the floor Amount of fresh air calibrated with number of study participants
Temperature	Usually set at 24–26 °C, fluctuating only within 0.5 °C Stable temperature reached 15 min after the start of the challenge session Recorded online every 5 s at four locations around the chamber at a height of 2.2 m
Humidity	Usually set at 40–45%, fluctuating only within 1.5%
CO ₂ concentration	Kept within 0.1% during challenge session, regardless of number of subjects and duration of session Recorded online every 5 s at a single location, 0.5 m above the floor
Pressure	60 Pa lower in chamber than on the outside, to prevent contamination of the working area or other parts of the building
Allergen dispersion system	Second air circuit for allergen-loaded air, with separated supplying system for different allergens to avoid cross-contamination Delivered by vacuum pressure from two locations on the ceiling Slow and continuous sedimentation of allergens occurs (e.g. 1 m/min for grass pollen)
Allergen load monitoring	Allergen load is constant within an SD of 5% over a 6 h session Target concentration is generally: pollen: 1500 grains/m ³ (700–2000 grains/m ³) dust mites: 20–110 ng <i>Der p 1</i> /m ³ Monitored using: modified Burkard pollen traps – simultaneous volumetric measurements (allergen particles/m ³) made at three levels and at nine different spots in each level, every 5 min. Thermo-anemometer automatically monitors the flow of the trap; slides automatically analyzed by light microscope cyclone samplers – accumulate and measure content of major allergen (ng). Immunohistochemical analysis using an enzyme-linked immunosorbent assay (ELISA) is performed Laser nephelometry – continual monitoring of the number of particles of certain diameters in the air

Der p 1, Dermatophagoides pteronyssinus.

symptoms and the efficacy and safety of experimental drugs. The effectiveness of oral antihistamines, nasal corticosteroids, immunotherapy and ocular compounds are just some of the investigations conducted in ACCs and published in peer-reviewed journals to date (Table 9).

As would be expected, the types of symptoms assessed, the questionnaires used for data recording, the duration of a challenge session, the allergen concentration selected and other parameters vary between studies; each study and each chamber may have a different protocol.

Homogeneous allergen distribution. ACC studies typically involve exposure to a single allergen and subjects are exposed to the specified allergen during multiple sessions in an ACC. Inter- and intra-session allergen concentrations must be equivalent throughout multiple sessions within a study. In the VCC, for study protocols using different allergens, separate supply systems are installed

for each allergen type in order to avoid contamination. Dispensers supply the chamber with allergen-loaded air at a constant rate, and a regulated, slightly turbulent airflow ensures homogeneous dispersion of allergen in the air. A feedback system prompts dispensers to add or recirculate allergens to maintain a constant level within the chamber.

The pollen load in an ACC is carefully controlled and its homogeneity is tested by frequent sampling throughout the room. For example, Fig. 5 shows the distribution of pollen in the VCC, which is within a narrow range in all areas of the chamber. Once subjects are seated in the chamber, the pollen distribution system is switched on (at $t = 0$ h). The output of the pollen distribution system is then adjusted based on subsequent sampling to achieve a steady state, which ensures homogeneous dispersion of allergen throughout the chamber. This has been demonstrated in the ACC in Hannover, where extensive

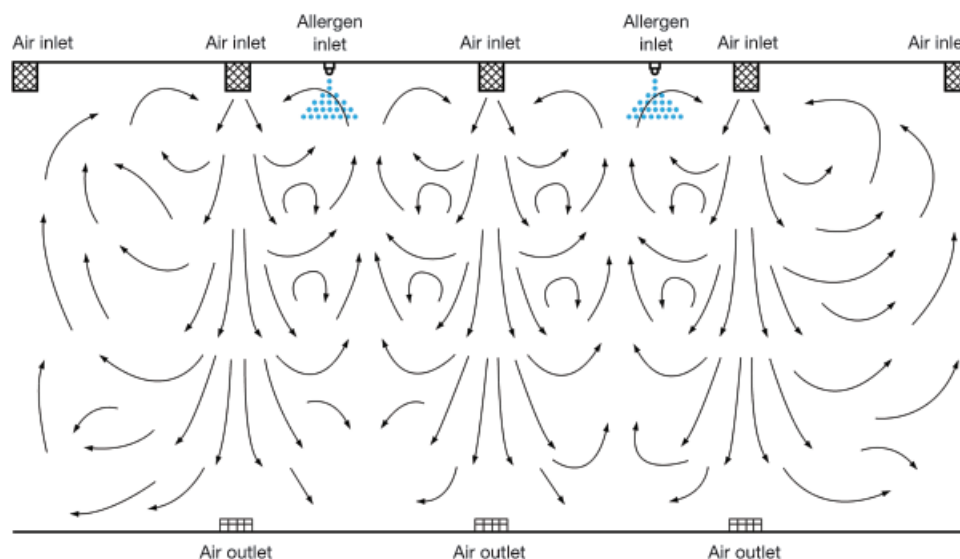


Fig. 2. Schematic to show turbulent airflow within the University Clinic Vienna Challenge Chamber to ensure uniform distribution of allergens.

Table 8. Key features of the Kingston Environmental Exposure Unit (EEU)

Feature	Specification
Chamber	Modified room in a hospital setting Volume: 924 m ³ Seating area takes up about one-third of floor space
Number of participants	Up to 160 100–120 is ideal for longer study periods
Ventilation system	100% outdoor air is drawn in and passes through Farr 30/30 and Farr Riga-Flo 200 filters Filtered air enters the chamber at four inlets each measuring 30 × 8 in, with a rate of 3200 cfm
Temperature	Maintained at 21–24 °C
Humidity	Maintained at 35–60% humidity
Pressure	Air balancing between EEU and adjoining room maintains a slightly lower pressure in the EEU, to minimize allergen loss
Allergen dispersion system	Pollen feeder emits pollen into the unit; modified laser counter measures the grains emitted and monitors the output of the allergen dispersion system Counter-clockwise circulating air stream is generated by groups of directional and box-type fans
Allergen load monitoring	Seven Rotorod counters (Sampling Technologies, St Paul, MN, USA) are arranged in and around the seating area (Figs 3 and 4), taking samples for 30 s every 30 min In response to these data, pollen emission from the feeder can be minutely adjusted to keep the pollen levels within a narrow range Ragweed pollen concentrations from 200 to 10 000 grains/m ³ have been used; 3500 ± 500 grains/m ³ is a commonly used concentration

cfm, ft³/min.

validation measurements have demonstrated homogeneous spatial pollen distribution within a range of ± 10% [88].

Allergen types. For the investigation of SAR, allergens used commonly include pollens from grass (e.g. *Phleum pratense* or *Dactylis glomerata*), birch tree (*Betula pendula*), ragweed (*Ambrosia elatior* or *Ambrosia artemisiifolia*) and Japanese red cedar tree (*Cryptomeria japonica*). The allergen to which most subjects with rhinitis are sensitive will vary between areas, with grass and birch pollens being key triggers in Europe [126], compared with rag-

weed, grass and tree pollens (birch, maple and oak) in North America, and Japanese red cedar pollen in Japan. The size, concentration and allergenicity (antigenicity) of pollens all play a role in the sensitization of subjects, and so pollen species and concentration are controlled for in an ACC study. Commercial ragweed pollens are available and have been shown to have the same allergenicity as fresh pollen. The same batch of pollen, which is characterized antigenically (antigen E), is used throughout a given study in the EEU in Kingston. The FDA also provides a reference pollen extract, enabling determination of pollen allergenicity – the Bioequivalent Allergy Unit. For PAR,

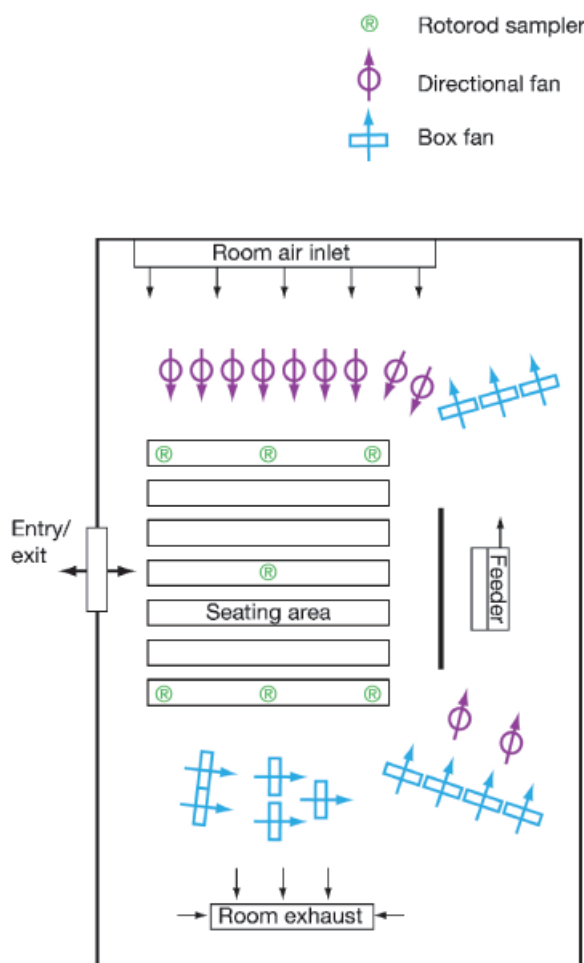


Fig. 3. Map of the Kingston Environmental Exposure Unit. Reproduced from Day and Briscoe, [92], with permission.



Fig. 4. The Environmental Exposure Unit at Kingston General Hospital, set up in preparation for a challenge session. Supplied courtesy of J. Day.

HDM (*Dermatophagoides pteronyssinus*) *Der p 1* is used commonly.

Allergen concentration. In SAR trials, the aim of the ACC is to provide controlled allergen delivery at levels

consistent with peak outdoor exposures to elicit the full range of allergic symptoms (from mild to severe) in allergic subjects without producing symptoms in non-allergic subjects [92]. Sensitivity varies among individuals, but the intensity of symptoms in response to grass pollen, for example, appears to be concentration dependent [88]. In real life, subjects may be exposed to a wide range of allergen concentrations of up to 20 000 grains/m³ [127]. By using a constant level of allergen, differences in symptom severity during the study reflect differences in treatment efficacy and not differences in levels of allergen or exposure.

Studies in subjects with PAR require allergen challenge with, for example, HDM products. Usually, the allergen content of a room is defined by carpet and floor dust samples [128, 129]. However, HDM allergens can become airborne and the levels of *Der p 1* (the major dust mite allergen) are important for sensitized individuals. Concentrations of 0.03–30 ng/m³ have been reported in different households, and the threshold value for sensitized subjects is around 10 ng/m³ [130]. Peak concentrations of 50–110 ng/m³ *Der p 1* are used in ACCs [94, 110, 131], as an increased risk of bronchial attacks would be expected at levels above 130 ng/m³ [132]. However, owing to the instability of particles containing HDM allergens, simultaneous immunohistochemical analysis is necessary to confirm the allergenic load [132].

Conducting clinical assessments

Study design and target parameters. ACC studies can be used for several evaluations, including:

- basic science, e.g. clinical relevance of mediator release in nasal secretions;
- priming effect, using repeated challenge sessions on consecutive days;
- exploring the time-course of symptom recovery following the end of allergen exposure;
- proof-of-concept for a compound in early Phase II;
- dose-finding for a new compound;
- onset of action of a single dose of medication;
- duration of action of a single dose of medication;
- efficacy during the late-phase allergic reaction;
- efficacy of a single dose of medication, compared with placebo and an active control;
- efficacy of a drug in steady state after 1 week of treatment, compared with placebo and an active control;
- comparison of efficacy among two or more rhinitis agents in the same class;
- safety and tolerability;

Table 9. Peer-reviewed publications on trials conducted in allergen challenge chambers in allergic rhinitis

Reference	Allergen	Trial design	N	Focus of trial
Horak et al. [100]	Grass pollen	Three-way, double-blind, crossover	6	Onset and duration of the effects of astemizole, loratadine and terfenadine forte in rhinitis
Horak et al. [101]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	12	Efficacy, duration of action and dose-finding of a sustained-release dimethindene formulation in rhinitis
Horak et al. [102]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	7	Effects of astemizole on nasal obstruction in atopic patients
Horak et al. [103]	House dust mites	Randomized, double-blind, placebo-controlled, crossover	12	Controlled exposure to dust mite allergen in a dose-finding study of DMM in dust mite-allergic patients
Horak et al. [104]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	12	Dose-finding study of sustained-release DMM
Horak et al. [105]	Grass pollen	Randomized, double-blind, single-dummy, crossover	12	Efficacy (onset of action and duration of drug effect) and tolerability of astemizole-D and loratadine-D in rhinoconjunctivitis
Horak et al. [51]	Grass pollen	Randomized, placebo-controlled, double-blind, crossover	24	Quantification of conjunctival vascular reaction by digital imaging, using azelastine or placebo in grass pollen-allergic patients
Day et al. [106]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel group	85	Onset of action of aerosolized triamcinolone acetonide nasal spray in seasonal allergic rhinitis
Donovan et al. [85]	Ragweed pollen	Controlled	43	Efficacy of > 2 years of ragweed immunotherapy for preventing rhinitis symptoms, compared with non-ragweed-allergic subjects or ragweed-allergic subjects who received no immunotherapy
Kyrein et al. [107]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	12	Efficacy of intranasally applied DMM solution as spray, compared with placebo and azelastine, in seasonal allergic rhinitis
Day et al. [108]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel group	111	Onset of action and efficacy of terfenadine, astemizole, cetirizine and loratadine in seasonal allergic rhinitis
Day et al. [109]	Ragweed pollen	Randomized, double-blind, single-dose, placebo-controlled, parallel-group	99	Onset of action, efficacy and safety of a single dose of fexofenadine hydrochloride or placebo in seasonal allergic rhinitis
Day et al. [46]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel-group	202	Efficacy and onset of action of cetirizine, loratadine or placebo in seasonal allergic rhinitis
Horak et al. [110]	House dust mites	Randomized, double-blind, placebo-controlled, crossover	24	Efficacy and safety of an oral formulation of cetirizine with sustained-release pseudoephedrine, relative to placebo, in perennial rhinitis
Horak et al. [111]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	24	Efficacy and tolerability of azelastine eye drops against pollen-induced allergic conjunctivitis
Horak et al. [112]	Birch pollen	Randomized, double-blind, placebo-controlled, parallel group	41	Efficacy and tolerability of short-term immunotherapy with sublingual birch pollen extract in rhinoconjunctivitis
Horak et al. [50]	House dust mites	Double-blind, placebo-controlled, crossover	12	Effect of continuous allergen challenge on clinical symptoms and mediator release in dust mite-allergic patients, and effect of loratadine
Ellis et al. [90]	Ragweed pollen	Repeated quality of life questionnaires	219	Investigation of possible effect of participating in an allergen challenge research trial on quality of life
Day et al. [31]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel-group	217	Onset of action of intranasal budesonide compared with placebo in seasonal allergic rhinitis
Horak et al. [113]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	36	Efficacy and tolerability of intranasal DMM solution vs. placebo in seasonal allergic rhinitis
Day et al. [47]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel-group	360	Comparative onset of action and symptom relief with cetirizine, loratadine or placebo in seasonal allergic rhinitis; methodological validation study
Ellis et al. [53]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel group	209	Investigation of whether quality of life indices are predictive of placebo and medication response to treatment for allergic rhinitis in a study of budesonide and placebo

Table 9. Continued.

Reference	Allergen	Trial design	N	Focus of trial
Horak <i>et al.</i> [99]	Grass pollen	Investigator-blinded, placebo-controlled, crossover	40	Comparison of the efficacy and safety of cetirizine, 10 mg o.d., and fexofenadine, 120 mg o.d., in seasonal allergic rhinitis
Stübner <i>et al.</i> [114]	House dust mites	Randomized, non-blinded, crossover	36	Efficacy and safety of cetirizine plus pseudoephedrine and xylometazoline nasal spray in patients with perennial allergic rhinitis
Horak <i>et al.</i> [87]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	47	Effect of desloratadine vs. placebo on nasal airflow and subjective measures of nasal obstruction in seasonal allergic rhinitis
Horak <i>et al.</i> [115]	Grass and ragweed pollen	Randomized, double-blind, placebo-controlled, four validation trials	493	Comparison of the effects of desloratadine, 5 mg o.d., and placebo on nasal airflow and seasonal allergic rhinitis symptoms induced by grass pollen and ragweed pollen exposure, respectively
Berkowitz <i>et al.</i> [95]	Ragweed pollen	Randomized, single-dose, double-blind, placebo-controlled, parallel group	298	Onset of action, efficacy and safety of fexofenadine, 60 mg/pseudoephedrine, 120 mg, vs. placebo
Wilken <i>et al.</i> [98]	Ragweed pollen	Randomized, parallel group	296	Effect of having symptomatic (allergen-exposed, <i>n</i> = 234) or asymptomatic (non-allergen-exposed, <i>n</i> = 62) allergic rhinitis on vigilance and cognitive functioning
Wilken <i>et al.</i> [116]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel group	204	Comparison of the efficacy of diphenhydramine and desloratadine and their effects on vigilance and cognitive function
Horak <i>et al.</i> [86]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	46	Comparison of the effects of desloratadine, 5 mg o.d., and placebo on nasal airflow and seasonal allergic rhinitis symptoms induced by grass pollen exposure
Horak <i>et al.</i> [117]	Grass pollen	Randomized, double-blind, comparative, crossover	37	Onset and duration of action of ketotifen 0.025% and emedastine 0.05% after repeated pollen challenges in seasonal allergic rhinoconjunctivitis
Horak <i>et al.</i> [118]	Grass pollen	Randomized, double-blind, two-treatment, two-period crossover	47	Efficacy and safety of ketotifen eye drops as adjunctive therapy to mometasone nasal spray in seasonal allergic rhinoconjunctivitis
Krug <i>et al.</i> [88]	Grass pollen	Two studies: Randomized, double-blind, crossover	23	Technique validation studies: Efficacy and safety of exposure to four different concentrations of pollen in patients with seasonal allergic rhinitis
		Randomized, double-blind, parallel-group, placebo-controlled	24	Reproducibility of efficacy and safety parameters in a study situation
Berkowitz <i>et al.</i> [119]	Ragweed pollen	Randomized, single-dose, double-blind, placebo-controlled, parallel group	486	Onset of action, efficacy and safety of fexofenadine, 60 mg/pseudoephedrine, 120 mg, vs. placebo
Day <i>et al.</i> [120]	Ragweed pollen	Randomized, double-blind, placebo-controlled, parallel group	575	Duration of effect of cetirizine and fexofenadine in seasonal allergic rhinitis
Day <i>et al.</i> [124]	Ragweed pollen	Randomized, double-blind, parallel-group, placebo-controlled	373	Efficacy and onset and duration of action of levocetirizine and desloratadine in seasonal allergic rhinitis
Stübner <i>et al.</i> [121]	Grass pollen, house dust mites	Randomized, double-blind, placebo-controlled, crossover	112	Efficacy and onset of action of levocetirizine and loratadine in patients with seasonal or perennial allergic rhinitis
Horak <i>et al.</i> [122]	Grass pollen	Randomized, double-blind, placebo-controlled, crossover	94	Onset and duration of action of levocetirizine and fexofenadine in patients with seasonal allergic rhinoconjunctivitis
Zieglmayer <i>et al.</i> [97]	House dust mites	Randomized, double-blind, two-treatment, two-period, crossover	36	Efficacy and safety of cetirizine plus pseudoephedrine and budesonide nasal spray in patients with seasonal allergic rhinitis
Krug <i>et al.</i> [123]	Grass pollen	Randomized, double-blind, parallel-group, placebo-controlled	165	Efficacy and safety of loteprednol etabonate nasal spray in patients with seasonal allergic rhinitis
Day <i>et al.</i> [125]	Ragweed pollen	Randomized, double-blind, placebo-controlled	599	Efficacy 5–12 h postdose of cetirizine and fexofenadine in seasonal allergic rhinitis

DMM, dimethindene maleate; o.d., once daily.

- short-term change in QoL parameters; (The impact of symptoms on QoL parameters, as well as the ability of subjects to concentrate and perform activities, will be influenced both by the allergic reaction and by the effect of the trial drug, which can be measured with appropriately designed questionnaires [90].)
- performance and productivity studies.

The number and duration of challenge sessions carried out for a trial will vary. As many of the studies to date have focused on determining onset of action, the duration of challenge sessions has generally been restricted to one to two sessions conducted over 1–2 days – this is sufficient for determining the onset and duration of action of a single dose of medication. However, it is feasible for protocols to involve a greater number of sessions separated in time: for example, in a multiple-arm crossover study [87]. A balanced crossover study can provide precise results with few subjects. In the VCC, 28 subjects have been found to give sufficient power in a two-arm crossover trial, but for a comparison of two or more active arms and placebo, the number of subjects must be increased accordingly.

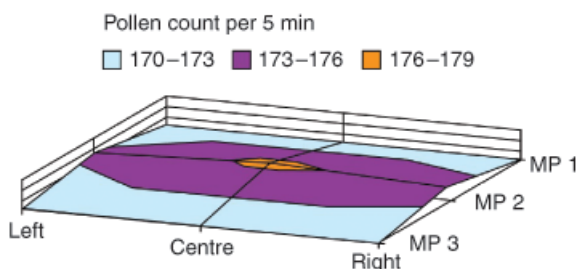


Fig. 5. Distribution of pollen load at a height of 1.5 m in the Vienna Challenge Chamber (grass pollen grains/0.2 m³). MP, measure points.

Subjects are typically exposed to allergens for between 4 and 10 h in an ACC study, which is consistent with daily exposure to pollen in a ‘real life’ setting. Data from trials investigating allergen exposures of up to 8 h in the VCC have shown that subjects’ symptoms remain stable throughout this time-period, allowing extended evaluation of medication efficacy [50].

Medication may be administered before or after the allergen challenge, depending on whether a treatment is intended to be taken prophylactically or as needed. However, in most cases, subjects ingest medication approximately 2 h following the beginning of antigenic challenge, if they achieve a predetermined qualifying symptom level. This baseline level of symptoms varies between studies, depending on the selection criteria specified by the protocol. The range of symptoms (mild, moderate or severe) selected for in the study population is important, so that if the treatment taken is effective, a decrease in symptoms can be observed.

Figure 6 shows an example of a study session in an ACC [46, 47]. Subjects remain in the EEU, in a pollen-containing environment, for 2 h to establish a baseline symptomatic state. The first dose of the trial medication(s) or placebo is administered and subjects are monitored regularly for the next 5 h. Subjects return the following day so that an end-of-dose (24 h) assessment of symptoms can be carried out before a second dose of medication or placebo is given.

The frequent, strictly timed evaluation of symptoms means that from the initiation of treatment until the 24 h period of expected efficacy, ACCs are one of the more clinically relevant methods to determine when the drug takes effect, as well as the duration of action and efficacy at other time-points over that period. ACCs are also well suited to the conduct of dose-ranging studies and proof-of-concept evaluations of medications in early clinical

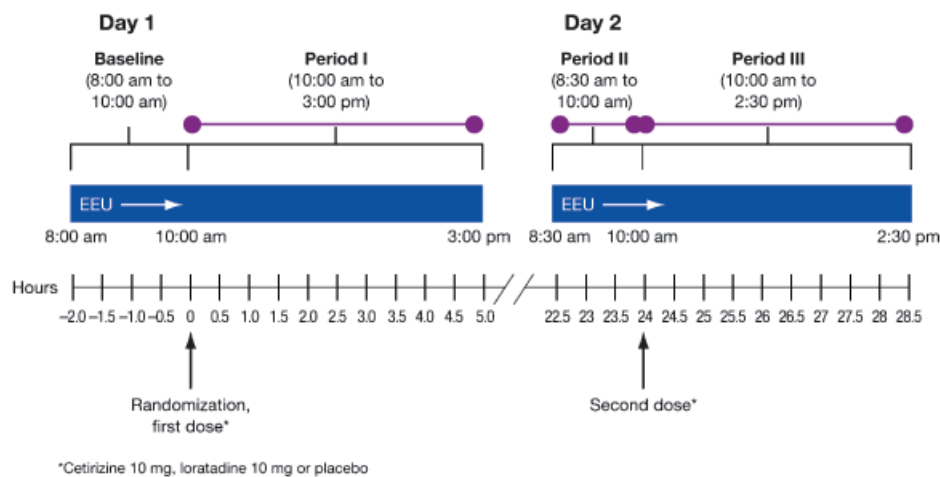


Fig. 6. Example of a protocol for comparison of cetirizine, loratadine and placebo in relief of allergic rhinitis symptoms in the Kingston Environmental Exposure Unit [46, 47].

development, as well as for direct comparisons of two or more medications.

Data collection and analysis. ACCs enable subjects' symptoms to be assessed separately and monitored from their inception until resolution. Missing values occur only where subjects discontinue a crossover trial or withdraw early following randomization.

On entering the chamber, subjects complete baseline symptom assessments. Depending on the chamber, subjects may record information directly into a computer (as in the VCC), or onto diary cards that can be read by an optical card reader (as in the Kingston EEU). Under the supervision of medical personnel, subjects then complete further self-assessments at regular intervals, depending on protocol requirements (e.g. every 15–30 min), rating the nature and severity of their symptoms. Subjects record the symptoms experienced at each time-point, with no recall or retrospective assessment required.

Subject-rated scores are still preferred as the primary measure of efficacy in AR trials [3]. However, in order to gather additional efficacy data from each session, objective measurements can be collected. It is possible to test skin response, lung function, nasal airflow, cellular mediators, blood levels of immune cells, nasal cytology or nasal secretion depending on the desired efficacy end-points. An advantage of the single-centre ACC setting is that the same apparatus and technique can be used to conduct these tests in all subjects; rhinomanometry, for example, is hampered in traditional trials by a diversity of instruments and procedures in multicentre settings. In an ACC, these examinations can be completed at a predetermined time, thereby allowing more accurate comparison between study groups.

Outcome measures are defined precisely in the protocol for each study conducted. Examples of outcome measures that can be achieved from ACC trials include the following:

- change in total symptom complex or individual symptom scores at a certain time-point, or over a period of several hours;
- time to onset of action;
- time to onset of 'clinically important' symptom relief;
- time to maximal effect;
- degree of symptom relief at 24 h/end of dosing interval;
- changes in respiratory parameters at 24 h (objective measures);
- changes in mediator release in nasal secretion (objective measures);
- the number needed to treat [133] for one subject to benefit;
- global evaluation of willingness to take medication again;
- global evaluation of satisfaction with treatment;
- change in QoL parameters;

- incidence of adverse events during entire treatment period.

The need to validate new methodology

For a given clinical trial, assumptions are made and limitations imposed, in terms of the inclusion/exclusion criteria used to enrol subjects, the conditions of medication administration and the methods of assessing response. In order to make clinical interpretations, it is necessary to assess the accuracy of results obtained in an ACC and to compare these with findings from other trial settings. There is a need to ensure that processes are consistent, results can be reproduced, comparisons can be made across trials and that increasing system complexity does not also increase the error rate. Additionally, validation of clinical findings compared with other standard methodologies is required to ensure scientific integrity of clinical data and to meet regulatory guidelines. Individual chambers should have their own supporting validation documentation. The VCC and the EEU in Kingston have been found to provide accurate and reproducible results, and to be valid instruments to assess the efficacy of anti-allergic medications [46, 47, 86, 87, 121, 134].

There are three main areas that require validation:

- the ACC itself;
- the computer systems used for capture and analysis of the data;
- the clinical trial processes used to ensure accuracy and reproducibility of results.

Fundamental to the ACC methodology are the following points, which will be described in more detail in the following sections:

- the intra- and inter-study allergen concentration should be constant;
- clinical findings in an ACC should be consistent when ACC protocols are repeated.

Constancy and reproducibility of allergen concentration. Allergen concentration is the most important parameter in the validation of a chamber because the principle that subjects are exposed to a well-defined stimulus is fundamental to the methodology. The spatial and temporal distribution of the allergen must be constant, giving equal exposure to all subjects for the duration of the challenge session. The allergen concentration varies widely in studies conducted in the natural environment, and reproducibility of conditions is impossible. The EEU and VCC have repeatedly demonstrated that a highly reproducible allergen level is attained not only between participating subjects within a cohort, but also for each cohort over the course of each study.

The following figures and tables provide examples to demonstrate that the allergen concentration:

- remains constant throughout the course of a single challenge session (Figs 7 and 8);
- can be reproduced within prespecified tolerance limits in subsequent sessions (Fig. 8 and Table 10);
- is maintained at a constant level, in contrast to variable allergen concentrations observed in other study settings (Fig. 9).

Reproducibility of clinical findings between studies. If conditions are controlled tightly within an ACC, repetition of the same protocol on separate occasions would be expected to yield the same results. For active treatment arms, although there is some variability in the magnitude of responses in different studies, the comparative efficacy

of each agent is highly consistent. Variability may be seen between placebo arms in repeated trials, but this is probably due to differences in study populations.

Desloratadine versus placebo. Two studies in the VCC investigated the effect of desloratadine on nasal congestion [86, 87]. In both studies, subjects received either desloratadine, 5 mg, or placebo for 7 days, followed by a 10-day washout period, before being crossed over to the other treatment for 7 days. Despite very small variations in the placebo response, the response to treatments is similar [86, 87]. In these studies, both the placebo and the medication data are highly reproducible across the studies (Table 11).

Cetirizine versus loratadine versus placebo. In the Kingston EEU, a study investigating relief of ragweed-induced

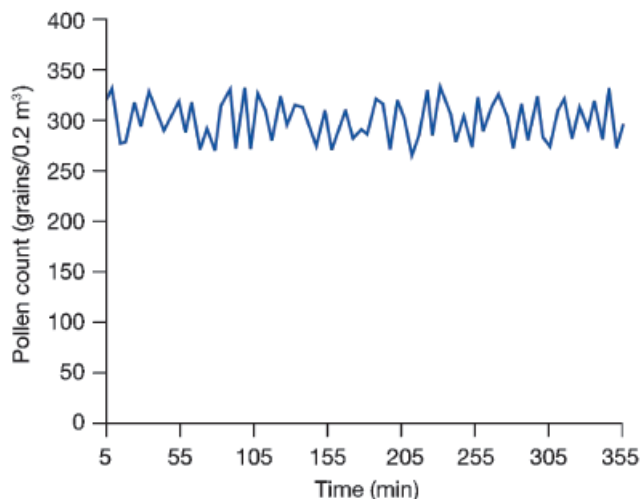


Fig. 7. Fluctuation of grass pollen load (approximately 5%) during a 6 h allergen challenge session in the Vienna Challenge Chamber.

Table 10. Reproducibility of grass pollen load in several sessions on consecutive days and weeks during 6 h challenge sessions conducted in the Vienna Challenge Chamber, with concentrations calculated every 5 min

Date	Pollen load (grains/m ³)				
	Mean	SD	Median	Minimum	Maximum
17 January 2000	1502	103	1493	1330	1700
18 January 2000	1490	102	1500	1325	1655
19 January 2000	1495	102	1500	1330	1670
20 January 2000	1502	107	1485	1340	1660
24 January 2000	1498	106	1510	1320	1655
25 January 2000	1497	101	1495	1320	1705
26 January 2000	1500	107	1505	1310	1695
27 January 2000	1496	100	1503	1325	1665
1 February 2000	1497	99	1493	1340	1690
2 February 2000	1506	104	1520	1335	1685
3 February 2000	1491	101	1488	1325	1670
4 February 2000	1487	98	1450	1330	1670

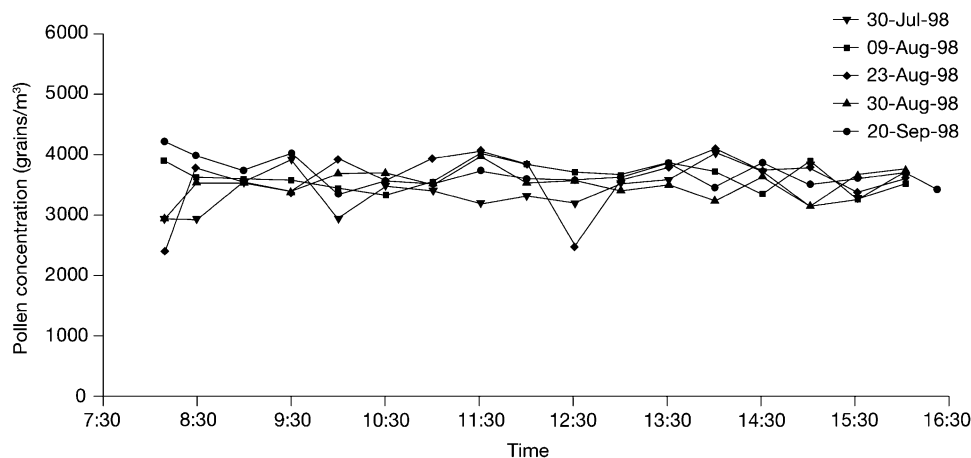


Fig. 8. Average 30 min ragweed pollen concentration in the Environmental Exposure Unit during separate study periods undertaken during the summer of 1998. Reproduced from Day and Briscoe [92], with permission.

AR symptoms with cetirizine, loratadine or placebo was conducted in August 1995 [46] and repeated in April 1999 [47]. The treatment schedule is shown in Fig. 6. Despite being conducted almost 4 years apart, the results were virtually identical in both studies. Although the treatment effect was slightly greater for all agents (including placebo) in the first study, the comparative efficacy was the same and the onset of action for cetirizine was 1 h compared with 3 h for loratadine in both studies (Table 12) [46, 47]. The only apparent difference between the two studies was the greater placebo response on day 2.

Symptoms in an allergen challenge chamber are similar to those obtained by other methods

Allergen challenge in an allergen challenge chamber results in a similar symptom score to that obtained in a park setting, but with less fluctuation. In a study in the VCC (F. Horak, personal communication), subjects were challenged for 4 h with a grass-pollen load of 2000 grains/m³, then given an ocular challenge test (OCT) with a grass-pollen allergen solution. After 2 months, the same subjects repeated the study, except that they were challenged in a park setting for 4 h instead of in the VCC, and then given an OCT. Pollen levels in each setting are shown in Fig. 9. The VCC and park settings yielded closely matched results with respect to ocular itching for the 4-h study period, with less fluctuation in symptom score in the ACC setting (Fig. 10).

In the same study, conjunctival digital imaging was used to assess the impact of allergen challenge in the VCC

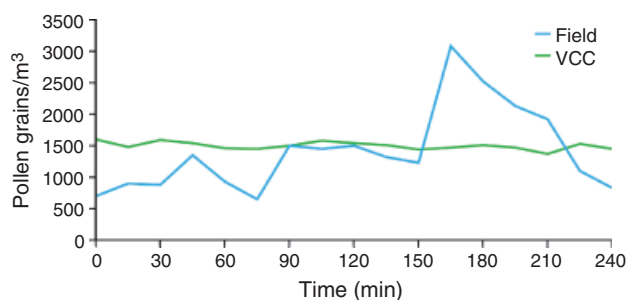


Fig. 9. Fluctuation of grass pollen count during 4 h in a park setting and in the Vienna Challenge Chamber (VCC).

and the park setting (Fig. 11), and the results were consistent.

Symptom scores with placebo or treatment in an allergen challenge chamber are of similar relative magnitude to those obtained by an ocular challenge test. In a dose-finding study using azelastine eye drops, the OCT was confirmed as giving similar results to the VCC [111]. In this double-blind, randomized, placebo-controlled, crossover trial, 24 subjects with a history of AR were challenged out of season with a single dose of azelastine 0.025%, 0.05% or 0.1% eye drops. The drops were administered 60 min before a 4 h challenge session, and an additional OCT was

Table 12. Comparison of key findings in a protocol repeated within the Kingston Environmental Exposure Unit, in two studies conducted 4 years apart [46, 47]

	Cetirizine, 10 mg	Loratadine, 10 mg	Placebo
Mean change in TSC from baseline (%)			
Study 1	-36.7	-15.4	-12.0
Study 2	-25.4	-11.2	4.8
Onset of action (h)			
Study 1	1	3	-
Study 2	1	3	-

TSC, total symptom complex.

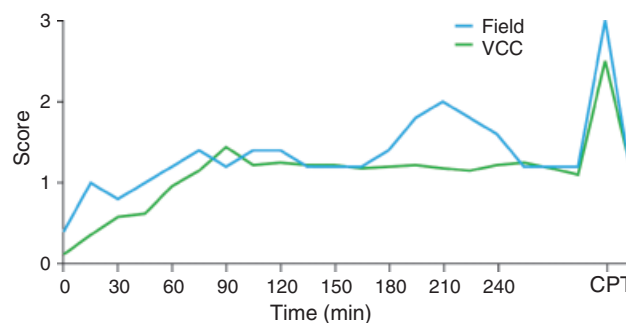


Fig. 10. Comparison of subjective eye itching using the conjunctival provocation test (CPT). This symptom was scored every 15 min on a 0–3 scale, in subjects studied in the Vienna Challenge Chamber (VCC) or in a park setting.

Table 11. Reproducibility of symptom scores across two consecutive studies in the Vienna Challenge Chamber using identical protocols but different subjects [86, 87]

	0–2 h				0–6 h			
	Active		Placebo		Active		Placebo	
	Study I	Study II	Study I	Study II	Study I	Study II	Study I	Study II
Nasal secretion weight (g)	0.53	0.5	1.41	1.6	1.87	1.8	4.7	5.3
Rhinorrhoea score	1.5	1.7	2.8	2.7	5.4	6.1	9.9	9.5
Total nasal score	6.1	6.1	10.6	10.5	22.5	22.1	38.1	37.8
Total non-nasal score	2.0	1.8	4.0	3.1	8.0	6.7	14.8	12.6

administered at the end of the session. There were 4 study days, each separated by a 2-week washout period. The use of 0.05% azelastine for the treatment of allergic conjunctivitis was supported by the sum of the VAS scores for itching of the eyes (Fig. 12) and lacrimation (Fig. 13), and the degree of vascularization (data not shown) obtained from VCC and OCT methodology [111].

Criticisms of allergen challenge chambers

As with other experimental models used to study AR and its treatment, the ACC model has been subject to critical analysis from the scientific community. Actual and hy-

pothetical criticisms are indicated and addressed in the following section.

Allergen challenge chambers do not represent 'real life' conditions. Despite their ability to provide highly controlled efficacy, safety and pharmacological data, studies conducted in ACCs have been criticized as not representing 'real life' conditions, leading to debate about whether conclusions drawn from these trials are clinically relevant. While allergic subjects participating in ACC studies are not exposed to the sensitizing allergen as in their natural, 'real life' environment, they regularly report that symptoms elicited in the EEU, an ACC setting, are similar to those experienced during the pollen season. This observation was confirmed recently in a survey in which subjects completed an assessment of their allergic symptoms in ragweed season, and again while participating in a trial conducted in the EEU [135]. Additionally, the activities that subjects engage in when in the EEU are similar to those encountered in a 'real life', 'at home' setting: subjects are free to watch movies, read or perform other activities while seated. Subjects may also briefly leave the seating area to stretch, obtain food and refreshments, and go for toilet breaks [44].

A single allergen source is used in an allergen challenge chamber. As a number of allergens and environmental factors may contribute to an individual's development of rhinitis, it has been argued that the single allergen exposure that is typically used in an ACC setting may not reflect the natural pathological process. At the molecular level, however, AR is initiated by the interaction of allergen with specific IgE. This is followed by immediate histamine release and then by other cellular events, which result in the clinical manifestation of AR regardless of the type or number of allergenic triggers. An atopic individual may develop AR as a result of single or

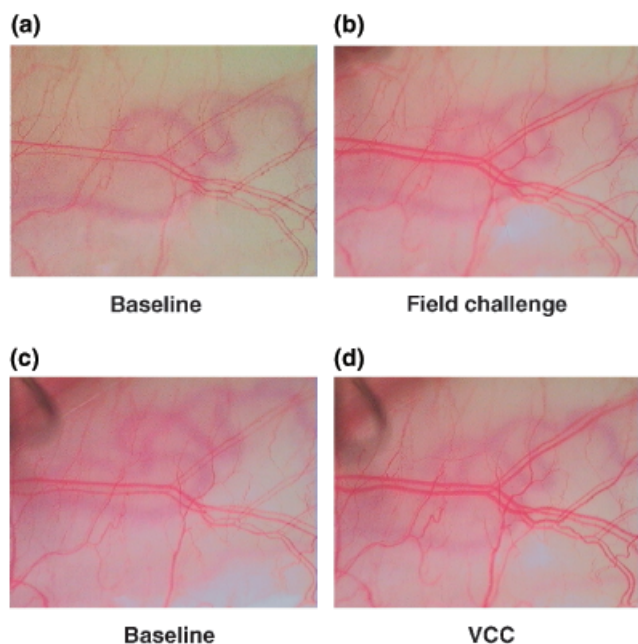


Fig. 11. A comparison of conjunctival reaction, as assessed by the hue saturation value (HSV), to allergen challenge in the Vienna Challenge Chamber (VCC) or in a park setting. Supplied courtesy of F. Horak.

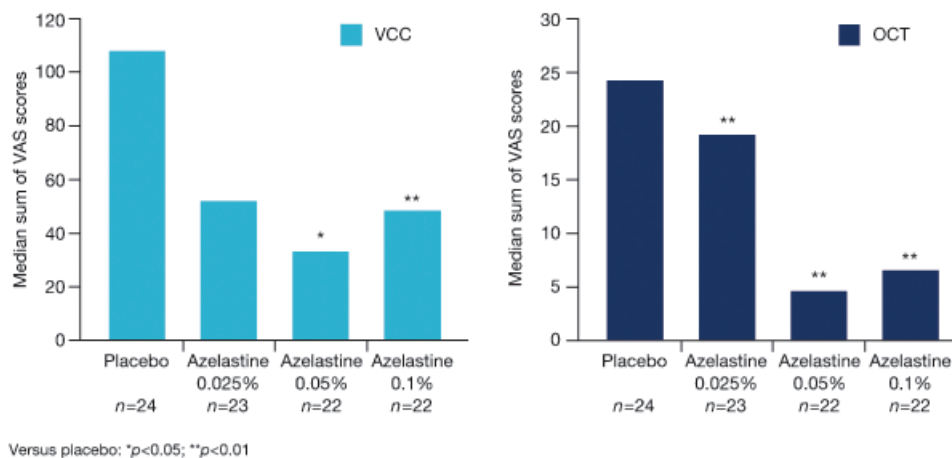


Fig. 12. Sums of visual analogue scale (VAS) scores for itching of the eyes at each time-point per treatment during the Vienna Challenge Chamber (VCC) sessions and 15 min after ocular challenge test (OCT). Reproduced with permission [111].

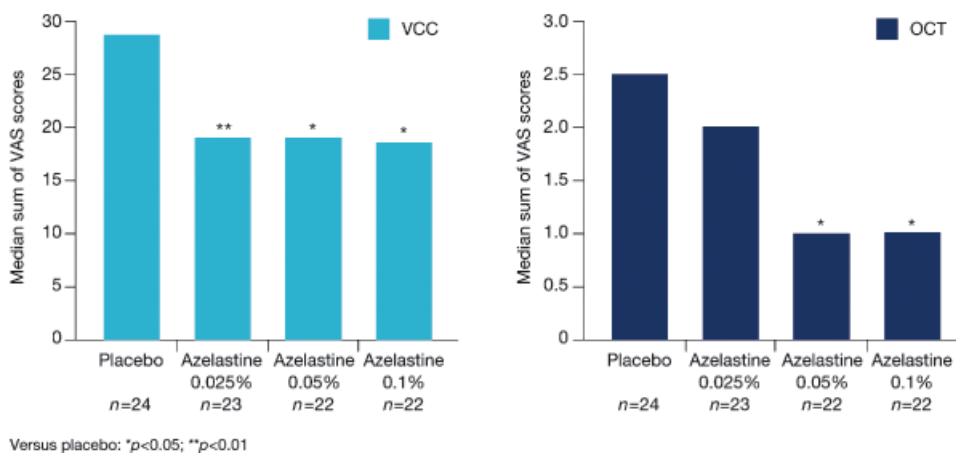


Fig. 13. Sums of visual analogue scale (VAS) scores for lacrimation at each time-point per treatment during the Vienna Challenge Chamber (VCC) sessions and 15 min after ocular challenge test (OCT). Reproduced with permission [111].

multiple allergen sensitivity. Therefore, it follows that the results obtained on the efficacy of anti-allergic medications derived from ACC studies using one allergen are transferable for the treatment of AR caused by sensitivity to different allergens. Additionally, as a single allergen can produce the full spectrum of symptoms required to evaluate an anti-allergic medication, the logistics of presenting multiple allergens would complicate a study unnecessarily.

Seasonal priming does not occur in an allergen challenge chamber. An allergic individual's reactivity to a seasonal allergen should increase within a season because of the priming effect [21]. Additionally, priming by one allergen appearing early in the season may induce sensitivity to another allergen appearing later in the season. It is argued that the priming effect is overlooked in ACC studies when they are conducted out of season. This leads to the assumption that the reactivity of participants to allergens in an ACC setting may differ from that observed in a natural environment.

However, ACC studies are not limited by season and may be conducted at any time of the year, for both non-seasonal and seasonal allergens. Subjects enrolled in ACC studies, like traditional studies, have a well-documented history of SAR and/or PAR (where applicable), are screened for sensitivity to the test allergen by skin testing and are then exposed to the allergen at a predetermined level in the priming phase in order to activate allergic reactivity. Only those subjects who demonstrate adequate symptomatology required by a study protocol are later challenged and randomized to receive double-blind medication. As long as the allergen is being delivered, the priming effect persists throughout a study [99].

During crossover trials at the University Clinic VCC, a washout period of 8–10 days between individual challenge sessions is often included to avoid the priming effect

within a trial. However, the priming phase is an important element in the study design of all EEU (Kingston) studies and is included whether studies are undertaken in or out of season. Reactivity to the challenge allergen awakens dormant responsiveness in the priming phase, leading to adequate symptoms on the study date.

As in traditional or park studies, ACC studies may be influenced by both seasonal and non-seasonal priming. With all three types of study, the degree of a subject's exposure to other sensitizing allergens is variable, as the level of previous environmental exposure cannot be controlled. Priming is a complex process that occurs in nature and in the ACC setting, and manifests as typical allergy symptoms. The rate and severity of symptom development during priming is a phenomenon that is currently being studied in the ACC setting [24].

The allergen concentration in an allergen challenge chamber is not 'natural'. There is concern that the levels of allergen maintained in an ACC setting are higher than those experienced by allergic individuals in their 'natural' environment. Daily environmental pollen levels that are reported as a 24 h average are obviously downwardly influenced by the pollen-low hours of the night. Furthermore, pollen service lines measure pollen from a height of 15 m. However, pollen concentrations at 1.5 m above the ground have been found to be much higher, and, therefore, the daily average count from a service line must be multiplied by 11–26 to compensate for these differences [136], which are compounded by the reality that service line readings are usually taken far from trees and other local pollen sources [137].

A concentration of 2000 grass pollen grains/m³ air used in the VCC corresponds with 75–180 grass pollen grains/m³ air measured as a daily mean concentration at a height of 15 m. Concentrations in excess of 1000 grass pollen grains/m³ have been reported at 20 m, which

indicate higher counts at ground level [65]. In the EEU setting, a target ragweed pollen concentration of 3500 ± 500 grains/m³ is consistent with peak outdoor levels reported by others [71, 138]. Thus, allergen concentrations in an ACC are comparable with peak environmental levels found during the pollen season.

Dose-dependent relationships between the total nasal symptom score, nasal flow rate and nasal secretions with pollen levels ranging from 1000 to 8000 grains/m³ have been observed by Krug et al. [88] in their ACC. These are at levels in or above the upper range of naturally occurring grass pollen. As symptom levels are known to fluctuate with changes in pollen levels, traditional trials are scheduled during the peak of the pollen season when symptoms should be present over the duration of the study [81]. The relationship between allergen concentration and symptom induction highlights the importance of using pollen levels within upper environmental ranges to facilitate sufficient symptom induction. ACC studies can emulate the peak of the allergy season, which is only encountered irregularly in traditional and park studies and, in this context, the US FDA has indicated that ACC studies may be used to evaluate anti-allergic medications for the prophylactic treatment of SAR [3].

The diurnal variation in pollen levels existing in nature is not seen in a controlled setting, and this has been challenged as a potential limitation of ACC studies. However, diurnal variation in pollen levels inherent in park studies has led to concerns about irregularity in symptom intensity [71]. In this respect, different times of onset of action were reported for the same treatment, at sites that had varying levels of pollen in a multisite park study [75], leading to the speculation that differing levels of pollen were responsible. The EMEA requires the degree of exposure of subjects to allergens during the study to be documented, to address the possibility that an improved symptom score may be due to spontaneous improvement, or declining or absent allergen exposure rather than treatment effect [4]. Both the EMEA and the FDA indicate that for multicentre SAR trials, pollen levels should be measured at each study centre [3, 4]. The significant shortcoming of variable pollen exposure in traditional trials and park studies is eliminated in ACC studies: for a given study population, which may be comprised of multiple cohorts, each cohort and each subject within a cohort is predictably exposed to the same levels of pollen, providing the desired consistency of pollen exposure for studies involving both small and large numbers of subjects.

Subjects in an allergen challenge chamber are affected by the trial context. It has been suggested that subjects participating in ACC studies, like those in park studies, interact with other trial subjects, which may influence their experience or reporting of symptoms. Results ob-

tained in ACC studies have been shown to be reproducible and to discriminate between treatment and placebo, indicating that subjects record their symptoms accurately. This is exemplified by two EEU trials, identical in design but conducted years apart, which evaluated the comparative onset of action of cetirizine and loratadine. In the first trial, undertaken in 1995, 202 allergic subjects were exposed to ragweed pollen for 7 and 6 h, respectively, on 2 consecutive days, where they were randomized to receive daily doses of cetirizine, 10 mg, loratadine, 10 mg or placebo [46]. Cetirizine produced a 37.4% mean reduction in MSC scores vs. 14.7% with loratadine, and 6.7% with placebo [46]. Onset of action, as assessed by a reduction in MSC and TSC scores vs. placebo, was evident within 1 h for cetirizine and 3 h for loratadine. The second study, which included 360 subjects, was completed in 1999, and showed comparable efficacy and identical onset of action [47].

Another concern raised against the trial context in which subjects are gathered together in a similar environment is the likelihood of greater placebo response because of the expectation of a beneficial effect of therapy [81]. Subjects are made aware during the consent process, as well as at other times over the duration of the study, of the random allocation of placebo or treatment to each and every participant. Placebo response rates in ACC trials have been found to be comparable with those observed in traditional trials [139, 140], but have also been found to differ depending on whether treatment is applied orally, topically or by injection [113, 122], which should also be considered in the trial design.

Subject demographics are limited in allergen challenge chamber studies. A limitation of ACC studies is that the pool of subjects available to participate is restricted to the catchment area of existing ACCs. This could be a problem in geographic regions with a limited ethnic population and, where it is, this could be addressed by including university students or deriving study participants from a nearby major city.

Allergen challenge chamber studies are of short duration. ACC studies have typically been designed to evaluate the onset and duration of action of anti-allergic treatments. This information is essential to the efficacy of anti-allergic medications as determined by the ARIA/EAACI workshop group [141]. Based on the protocols, the duration of these studies has generally been relatively short, usually 1–2 days, and therefore these studies are not readily suited nor intended to explore extended long-term efficacy or safety of anti-allergic medications. However, ACC studies have also been designed to evaluate medications for protracted periods of time (i.e. 1–2 weeks), with subjects taking medication on a daily basis [86, 106, 123]. The duration of ACC studies can be readily extended to provide medication efficacy and safety data at a steady

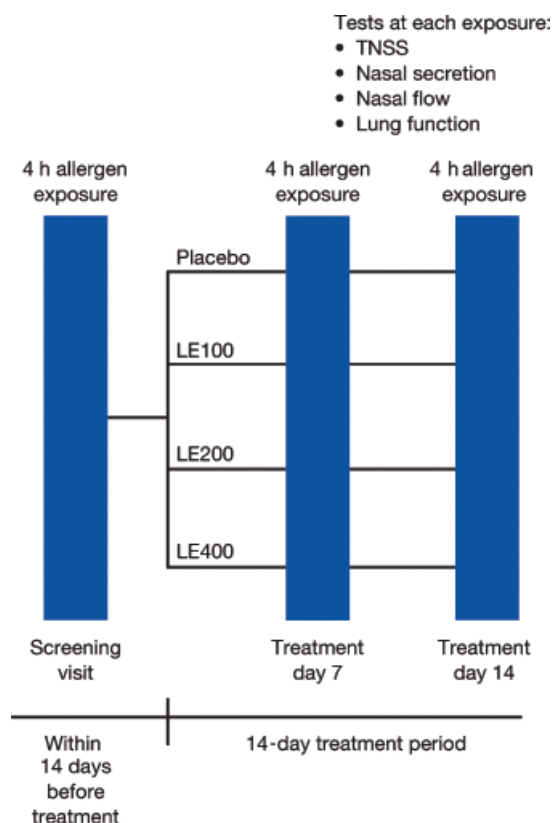


Fig. 14. Study design for investigation of the effect of loteprednol on seasonal allergic rhinitis. LE, loteprednol; TNSS, total nasal symptom score. Reproduced with permission [123].

state, whereby subjects are exposed to consistent levels of allergen on designated dates over the treatment period, without the variable allergen loads associated with park studies or traditional studies. In this type of study, subjects take the trial treatment at home and return to the ACC setting for subsequent allergen challenge in the coming days or weeks. An example of this kind of study has been published recently by Krug *et al.* [123] (Fig. 14).

The inflammatory stage of the allergic reaction can be readily studied in an ACC, in which long-term studies may be designed to evaluate pathophysiological events in chronic AR. The effect of medications on chronic symptoms can be explored in subjects sensitive, for example, to HDMS, as this perennial allergen occurs on a daily basis, year round, producing symptoms consistent with chronic exposure.

There is less experience with allergen challenge chambers than other methods. There is comparatively less experience with ACC methods than with other trial types, but as the number of ACCs increases to meet the rising demand for these studies, the body of experience will continue to expand. ACCs have been established for 20 years, and over 40 studies utilizing ACCs have been published in peer-

reviewed journals, producing clinically relevant data that complement those from traditional and other trials [44].

Summary and discussion

ACCs provide a valuable method for assessing anti-allergic treatments in a controlled and reproducible environment. The role of ACCs in the evaluation of new drugs being considered for development, as well as in comparative efficacy of approved anti-allergic medications is expanding. The increase in peer-reviewed publications reporting results of well-controlled ACC trials has led to discussion about the use of ACCs in a wider range of trial designs. At present, there are at least six established ACCs worldwide, three in North America and three in Europe; two ACCs are under development in Japan.

A better understanding of the capabilities of the ACC and its performance relative to traditional studies and other experimental models (e.g. NPTs and park studies) is needed for greater recognition by regulatory and scientific communities. Even with the large body of studies available in the current literature, a direct comparison of the various models is difficult because of the differing study designs used, including varied symptom scoring scales, timing of assessments, efficacy parameters and statistical plans. Nevertheless, a prospective comparison using each model in a similar study design would facilitate a rigorous analysis of their strengths and weaknesses and contribute to a better understanding of their capabilities [44]. The next step is the expanded use of the ACC in the evaluation of anti-allergic medications at steady state, in longer-term studies.

As indicated, the ACC offers many advantages and is especially suited to the utilization of the full spectrum of available methodologies for the assessment of treatment efficacy. This versatility is particularly advantageous for the exploration of new endpoints and innovative techniques, such as facial thermography [142, 143], which cannot be readily carried out in park or traditional studies. The combination of the controlled and reproducible environment of an ACC, together with its clinical relevance, will continue to contribute to a greater understanding of AR and its treatment.

Conclusions

Traditional outpatient studies are the accepted method of evaluating the efficacy of anti-allergic treatments for AR, as they represent the normal environment in which allergic subjects are exposed to allergen and treated for symptoms. These studies also address safety and measures of efficacy because of their long duration.

The variability of pollen counts in traditional outpatient SAR studies is given extensive consideration in the EMEA guidelines [4]. These guidelines acknowledge that the degree of allergen exposure may impact on efficacy and

that documentation of subjects' exposure to the relevant allergens is required to help determine whether an improved symptom score is a result of treatment effect, spontaneous improvement or insufficient allergen exposure. The rationale and requirement for a controlled environment is, therefore, substantiated. The clinically relevant ACCs have been established as a means to assess anti-allergic medications, based on their capacity to control a number of variables associated with traditional studies. Important parameters, such as onset and duration of action, as well as other precise measures of efficacy, are effectively determined with this method. This role in defining the onset of action of anti-allergic medications is recognized by the FDA [3], who also acknowledge the use of ACC studies in the evaluation of anti-allergic medications for the prophylactic treatment of SAR. Nonetheless, the role of ACCs, as acknowledged by regulatory bodies, remains secondary compared with traditional trials. The pharmaceutical industry also recognizes the value of ACC studies beyond their ability to evaluate precise measures of efficacy, including the requirement for fewer subjects over a shorter period of time because of the single-centre design of ACCs compared with traditional studies, with evident ethical advantages and financial savings.

This paper has reviewed the studies and physical features of ACCs and other methods to enable informed assessment of these models for the evaluation of treatments for AR. Highlights include the unique capability of ACC studies to produce and closely monitor symptoms from onset to resolution, and to implement methodologies for the objective measurement of efficacy when desired. The variability in inter-individual allergen exposure is eliminated, compliance with study drug is improved, and there is reliable and timely completion of symptom assessments.

When ACC studies of similar design are repeated, both in and out of season, and years apart, consistent outcomes are observed. Even though challenges are undertaken in an enclosed space because of the need to control allergen levels, the setting is conducive to subjects and researchers alike, and subjects readily equate symptoms to those experienced in the outdoors. In the case of the ACCs using pollen as the sensitizing allergen, the levels selected are intended to represent peak levels that are ordinarily observed outside during the pollen season. For example, the levels of ragweed pollen chosen for EEU studies are well within the outdoor range of peak levels and have the effect of producing the full spectrum of symptoms, from mild to severe, required to test anti-allergic treatments adequately. The ACC can also be adapted readily to long-term studies, in which measures of QoL and safety can be determined and important pharmacodynamic information obtained. There is much opportunity for further application of ACCs in the study of AR and its treatment, and this can be realized by innovative approaches that recognize the potential of these systems.

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