Clinical trial design, nasal allergen challenge models, and considerations of relevance to pediatrics, nasal polyposis, and different classes of medication

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Clinical trials in allergic rhinitis present several specific difficulties. In seasonal pollen-related disease, there are variations between subjects in the extent of pollen sensitization, individual variations in exposure to pollen even within a set area because of lifestyle differences, and variations between different areas in pollen counts and weather patterns. Thus, large patient numbers are needed in multicenter trials to account for such variations when the standard endpoint is symptom reporting. Furthermore, a pollen season may be relatively short (eg, lasting 6-8 weeks), and the pollen count is inconsistent during this period. Crossover study designs are thus inappropriate, and trials are usually conducted with a parallel-group design. This further increases the trial sample size as it reduces statistical power. These large patient numbers must be recruited over a very short period. Perennial house dust mite–sensitive allergic rhinitis presents other problems. Although there is less disease variation, it is appreciated that symptoms may be induced by nonallergic as well as allergic mechanisms because of the nasal hyperresponsiveness. The nonallergic symptoms may not be modified by treatments based on allergic disease mechanisms. Thus, symptom outcomes—although relevant to the patient—may not adequately reflect the pharmacologic efficacy of the specific intervention.

To control variability and focus on allergic disease mechanisms, nasal allergen challenge has been used in drug development. Single-dose challenges in the laboratory or in a pollen chamber, which allow many volunteers to be studied at the same time, have proven useful in the evaluation of drugs that afford acute symptom relief. However, such challenges incompletely model naturally occurring disease, in which the repeated daily exposure to allergen modifies the mucosal inflammatory cell profile and in particular promotes the epithelial accumulation of effector cells. This alters the response to allergen exposure. To model this, repeated low-dose daily allergen exposure has been used to generate these mucosal changes artificially, and early studies suggest that this may be a more valid model for the evaluation of anti-inflammatory therapy. However, little has been published with this model.

Different disease groups are associated with their own specific issues in clinical trials. The pediatric population, in which allergic rhinitis is common, has different requirements for education, quality of life evaluation, and adverse-event monitoring; nasal polyposis, because of the nature of the disease, requires additional means of assessment, such as nasal endoscopy and imaging (eg, computerized tomography scanning), as well as attention to additional outcome measures (eg, the measurement of sense of smell).

Within clinical trial design, there are important questions to be considered in relationship to the therapeutic intervention. Should this be given topically or systemically? What are the appropriate timing and frequency of medication? Does the disease itself modify the treatment efficacy, and does combination therapy afford better clinical outcome than single-modality therapy? These issues are discussed, and the influences of current therapies on objective outcome measures in allergic rhinitis are reviewed. (J Allergy Clin Immunol 2005;115:S460-82.)

Key words: *Clinical trial design, seasonal rhinitis, perennial rhinitis, intermittent rhinitis, persistent rhinitis, nasal allergen challenge, pediatric rhinitis, nasal polyposis, H_1-antihistamines, intranasal steroids, LTRAs*

The basic design components in clinical rhinitis trials may at a first glance seem fairly constant, but on closer inspection there are considerable variations. These reflect the need, under separate circumstances, to address different objectives, such as the effect of therapeutic interventions in preventing the development of seasonal allergic rhinitis (SAR) as opposed to reducing symptom

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Abbreviations used
CT: Computerized tomography
LTRA: Leukotriene receptor antagonist
NPIF: Nasal peak inspiratory flow
OME: Otitis media with effusion
PAR: Perennial allergic rhinitis
SAR: Seasonal allergic rhinitis

expression in established disease. The former may be more suitable for the evaluation of a novel intervention that would be anticipated to modify tissue cell recruitment than as a therapy that has purely symptomatic benefit. The study design thus needs to be tailored to the questions to be addressed. For example, with an appropriate study design, it has been possible to demonstrate dose-efficacy relationships for intranasal glucocorticoids in allergic rhinitis. Objective measurements can support the results acquired by subjective symptom scores and add value by increasing discriminative ability and confirming effects on inflammatory activity. Special considerations are necessary for different indications, and the existing classification of allergic rhinitis into seasonal and perennial is not always sufficiently helpful, whereas the classification of nonallergic rhinitis is recognized to account for a range of different nasal disorders with separate underlying pathophysiologic mechanisms. An awareness of the practical implications of clinical trial design and appropriate compromises between theory and clinical reality is necessary for a successful clinical trial performance. In this section, examples of considerations concerning the appropriateness of design in relation to the trial objectives and some related caveats are discussed. Specifically, this chapter starts with a discussion about general aspects of clinical trial design, progresses to challenge models, considers application in children, and finishes with a discussion about nasal outcomes in nasal polyposis and with different classes of medication used in the treatment of rhinitis.

GENERAL ASPECTS OF CLINICAL TRIAL DESIGN FOR RHINITIS

Patient populations

Once a clinical hypothesis and the objective are established, an appropriate study population needs to be determined. The criteria for the population are key, because the appropriateness of the population determines the validity of the results. The population should be a representative sample from a clinically relevant and identifiable population, typically identified by a common diagnosis. To achieve a conclusive result from a trial effectively, the enrollment criteria and the objective of the study need to be considered in concert.

Characterization: diagnosis and classification

The term *rhinitis* strictly refers to an inflammatory condition in the nasal mucosal lining. In daily practice, however, rhinitis is often colloquially applied to a typical symptom constellation, characterized by bouts of sneezing and nose running, with or without nasal itch or obstruction, and as such represents a clinical syndrome rather than a specific disease entity. In a wider sense of the term, any nasal mucosal modifications caused by, for example, pharmacologic effects, endogenous hormonal effects, or exaggerated physiological reactions, such as skier's nose, are also included under the term *rhinitis*. It is helpful to be aware of the shady overlapping borderline areas between nasal symptoms that are physiologically appropriate and those that cause discomfort and impair function, which constitute disease.

Primarily, rhinitis is classified as allergic or nonallergic. Allergic rhinitis is subdivided into seasonal and perennial or intermittent and persistent, dependent on the duration of symptoms.[1] However, the classification into intermittent and persistent is relatively recent, and trials are only now being undertaken using this classification. It is probable, however, on the basis of standard entry criteria and run-in periods, that most patients who enter clinical trials investigating the effects of regular medication in either seasonal or perennial rhinitis have persistent rhinitis. The basis for the change in classification from seasonal and perennial to intermittent and persistent relates to the appreciation that seasonal allergies in some parts of the world may indeed be perennial allergens in others. Furthermore, many patients have multiple sensitizations (Fig 1) and thus, although they are sensitized to seasonal allergens, their symptoms last longer than exposure to a single specific seasonal allergen. For example, there are perennial pollens, such as parietaria.[2] This makes a formal classification into seasonal or perennial rhinitis irrelevant, and recognition of intermittent and persistent allergic rhinitis is thus more relevant.[1] Secondary factors, such as severity of rhinitis, have been added to make the classification clinically useful for therapeutic guidance.[3,4] Similar approaches can be made to identify appropriate patient populations for clinical trial purposes.

Acquiring the population sample: confirmation of the diagnosis

Seasonal allergic rhinitis is a well-defined class of rhinitis with a distinct history easily confirmed by tests (skin prick, RAST, or provocation tests). Symptoms can be related to exposure with pollen counts, and biochemical and cellular indices of allergic inflammation can be confirmed by intranasal sampling techniques (eg, by nasal lavage or mucosal brushing). However, such an approach is not required to make the diagnosis, which is usually clear on the history.

In perennial allergic rhinitis (PAR), the diagnosis is based on a history of symptoms after relevant exposure and tests to confirm allergic sensitization, but sampling to measure exposure is not feasible in large-scale trials. In addition, many patients with perennial rhinitis have a mixed basis for their disease, with both allergic and nonallergic factors, such as structural airway abnormalities, contributing to the symptoms. For example,

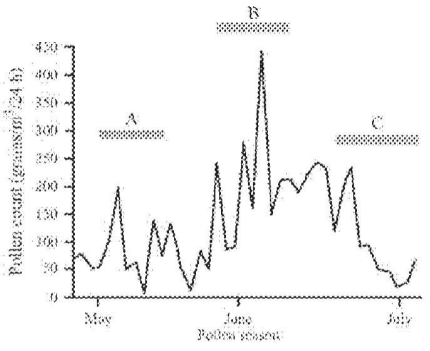

FIG 1. Seasonal changes in pollen count illustrating the potential effect of variation exposure on clinical trial outcome if studies are undertaken for 2 weeks at early in season **(A)**, at peak season **(B)**, and late in season as pollen count falls and symptoms spontaneously improve **(C)**.

a retrospective analysis of 975 rhinitis patients in the United States found that 23% could be classified as having pure nonallergic rhinitis, 43% pure allergic rhinitis, and 34% mixed rhinitis.[5] Accordingly, the magnitude of improvement with a therapeutic intervention in allergic rhinitis might be greater in those with pure disease than those with mixed disease. Thus, the majority of clinical trials of therapies in allergic rhinitis have focused on seasonal allergic disease.

Perennial nonallergic rhinitis is a diagnosis in which positive diagnostic criteria are often lacking. Subgroups are often insufficiently characterized even if discriminative indicators can identify a distinctive subgroup. For example, the presence of eosinophilic inflammation on intranasal sampling can lead to a diagnosis of nonallergic rhinitis with eosinophilia syndrome in subjects with rhinitis without specific IgE to common aeroallergens. Sensitivity to specific agents, such as aspirin, can occasionally be confirmed by provocation tests. Still, regardless of extensive efforts, on numerous occasions, perennial nonallergic rhinitis will be diagnosed on the basis of presence of symptoms in the absence of positive allergy tests or conclusive history.

Compromise between scientific theory and reality

Design considerations may lead to conflict between scientific ambitions and realities in clinical practice and, therefore, a need for compromise. The real-life situation in a patient consultation should be applied if the objective is to study drug efficacy. Under these circumstances, the patient's need for treatment may be the only relevant inclusion criterion. In a clinical situation, the history, a set of symptoms, and physical signs are sufficient for a therapeutic decision. However, this approach is not satisfactory in a scientific context in which measurable and verifiable data are wanted, and the diagnosis must be unambiguously confirmed. Scientific stringency and study management according to good clinical practice demand more precise diagnostic criteria.

Assessment of efficacy in clinical trials

Multiple factors contribute to variability in efficacy assessments. These include environmental factors such as allergen exposure, patient factors such as adherence, and treatment-related factors such as the intrinsic activity of the drug. Assessment of nasal symptoms is the mandatory clinical efficacy variable for evaluation of drug effects in rhinitis.

Symptom severity assessment

Assessment of efficacy in rhinitis is primarily based on subjective grading of symptom severity, as discussed in the section on clinical trial outcomes. Because symptom assessments are subjective, they are sensitive to factors that affect patients' experience of symptoms, including expectations, emotions, personality, personal perception, and basis of reference. Score step scales, such as rating scales or visual analogue scales, can be applied. Multiple symptoms are relevant and can be explored, but the mass-significance phenomenon must be kept in mind—that is, the risk that an abundance of variables can lead to chance findings and incorrect conclusions.

To minimize this risk, the number of efficacy variables should be kept at a minimum, preferably without compromising different aspects of the patient's experience. This can be accomplished by using a composite score which may consist of the 3 basic symptoms of rhinitis: (1) nasal blockage, (2) hypersecretion, and (3) the irritative sensory stimulus, presenting as nasal itch, or as its reflex response, sneezing. Typically, the 3 symptoms are given equal weight. Sometimes itch and sneeze are included separately, constituting a 4 basic composite symptoms score. With the latter approach, the irritative sensory symptom is weighed to at least 50% of the composite score, because rhinorrhea is also a symptom predominantly determined by sensory neural stimulation. The composites of the subjective assessments are not strictly independent variables; for instance, secretions may affect scoring for blockage.

The grading of symptoms can be based on severity or duration (hours per day). Assessments can be either instantaneous or reflective over a defined period (eg, last 12 hours). The former is necessary when precise time is relevant, as in onset or duration of action studies or with once-a-day medication, to verify 24-hour duration of therapy.[6] For subjective symptom scores, the information will always originate from the patient. Assessments are made directly by the patient or by the physician, but the latter will add filtering to the information.

It is also relevant to gather a more general assessment of efficacy. The global assessment of treatment efficacy and symptom relief by patients is a subjective assessment based on the patients' recollection and personal reference base. These are clinically relevant because they reflect the information clinicians use to evaluate efficacy of treatment at follow-up visits. The risk of recall bias and the lack of comparison with a baseline measure make this a less distinct variable. Nevertheless, it is a useful tool for

assessment of efficacy,[7] as is health-related quality-of-life (see the section on clinical outcomes).

Objective measurements

The reliability of subjective assessments is enhanced if they can be confirmed objectively. Among the objective methods, nasal peak flow offers daily measurements by patients at home (see the section on objective monitoring of nasal patency). Nasal peak inspiratory flow (NPIF) is an objective measure of nasal patency that can be used for home monitoring to link to the patient's experience of nasal congestion and gives a fair estimate of upper airway function with a coefficient of variation of around 10%.[8] Differences in efficacy between doses and drugs within a narrow interval can be detected by NPIF.[9] Other methods applicable in a large-scale situation are acoustic rhinometry and rhinomanometry (see chapter on nasal patency), but the added value of these more demanding methods over NPIF in large-scale trials has not been proven. The time of day and technique of measurement should be standardized and patients familiarized to procedures.

Nasal inflammatory indices can confirm the anti-inflammatory effects of an intervention (see section on objective monitoring of nasal inflammation).

Pollen exposure

An obvious external factor is exposure to allergen. Total absence of symptoms in pollen-sensitive patients with rhinitis out of season is followed by a priming period in which symptoms and reactivity to allergen gradually increase and continued exposure to allergen drives symptoms. Monitoring pollen counts in the areas where the study is ongoing gives only a very rough estimate of individual exposure. Pollen exposure can vary considerably, not only from one season to another but also day by day and from one place to another. Exposure is largely dependent on the weather conditions during the pollination period but also on individual factors. Patient-related factors like frequency and duration of outdoor activities, ability to avoid exposure, and individual reactivity will affect symptom severity. For example, 2 individuals within the same area, with comparable degrees of seasonal aeroallergen sensitization, will have different symptom severity if one has an outdoor job and the other works indoors. Personal monitoring of exposure, although possible, is technically complicated and not feasible in full-scale trials.

If the intrinsic efficacy of the drug under evaluation is a primary objective, as in dose-finding trials, it is helpful to control pollen exposure by only taking into account days with a minimum level of exposure. As an example, in a seasonal study where no difference between 2 nasal steroids was found in the overall analysis, an efficacy difference was detected on days with at least moderate exposure.[10] This indicates that sufficient exposure may enable detection of more subtle differences. The relevance of exposure is further illustrated by subanalyses in a trial conducted in 2 geographical regions. In one region, the ragweed pollen season was trivial, as confirmed by daily monitoring, and in the other region met the anticipations of the trial. In the latter, a significant dose-response was found in the subpopulation with low allergen exposure, and no significant differences were found within a 4-fold range of doses.[11]

Patients receiving effective treatment have a heterogenous response and could have decreasing, unchanged, or even increasing symptom severity, depending on circumstances and the starting point (Fig 1). Placebo is thus necessary to ensure relevant exposure. In the absence of placebo control, a lack of exposure can lead to false conclusions regarding efficacy.

Crossover versus parallel group design

A crossover design has the advantage that patients act as their own controls, and there is thus a need for fewer patients by eliminating interindividual variation, under the assumption that disease severity is comparable in all periods. This is suitable for studies in PAR with continuous symptoms, but not for continuous treatment trials in seasonal disease. Although randomization will balance differences between periods and sequence effects can be dealt with statistically, confounding because of environmental factors, mainly variations in pollen exposure in seasonal disease, can complicate interpretation of results and possibly eliminate the advantage of this design. The length of a crossover trial also introduces an added risk. A run-in period lasting from a few days to as long as a week is advisable to establish a solid baseline, followed by treatment periods lasting 2 to 3 weeks, separated by a washout period whose length is dependent on the drug under evaluation. Thus, even the simplest comparison of an active agent with its placebo will take 6 weeks and may endanger the comparability of treatment periods in a pollen season lasting 1 to 2 months.

Treatment periods may be subject to rising or falling pollen counts and varying sensitivity to treatment because of different stages of inflammation. For all of these reasons, there are theoretical advantages to a parallel-group design, making it preferable for most trials in SAR, with the caveat that larger numbers of patients are required compared with a crossover study.

Dose-response

If variation is minimized, the ability to detect the intrinsic efficacy of a drug and differences between doses is enhanced. PAR is a more heterogeneous population than SAR, and exposure to allergen can vary largely. Attempts to demonstrate a dose-response in PAR studies, in the sense that one dose is statistically significantly superior to another, often fail,[12] even if it is occasionally possible.[13]

Through the application of provocation models, such as the repeated nasal allergen challenge model to create a nasal allergen challenge artificial season, it has been possible not only to demonstrate dose responses[14] but also to compare efficacy between compounds.[15,16] Such models can be helpful to compare the clinical potency of different compounds.

Placebo effect and regression to the mean

A baseline period before start of treatment will offer the best reference when the change induced by treatment is of interest. It is not unique that the mean symptom severity progressively increases the week before start of treatment. There is a risk of a filtered population sample. If inclusion in the trial requires minimum symptom severity, patients scoring high, having bad days could be favored for inclusion. Patients included at the peak of symptoms in a condition where symptoms may vary spontaneously over time are not likely to get worse. The result will be a population that will have preponderance toward improvement. This improvement, which could be interpreted as efficacy, will also be seen in the placebo group, and this accounts for some of the improvement seen in the placebo group. Thus, for the evaluation of efficacy, comparisons with placebo are essential.

Rhinitis trials, in which primary efficacy variables are subjective, are especially sensitive to a placebo driven by expectations and bias. Clearly, there are effects of a nasal spray placebo, with as much as a 50% change from baseline with such therapy.[17] An aqueous nasal spray in itself is likely to be an active treatment rather than a pure placebo, because the mere moisturizing or cleansing effect of a nasal spray will dilute or wash out mediators and relieve symptoms. However, even with an oral placebo, a >30% reduction in symptom scores has been found in some studies.[18] A third factor that can contribute to efficacy in placebo groups is patients' use of other effective medications, either supplied rescue medication or undetected use of over-the-counter remedies.

Significance of findings

The size of the population sample will determine statistical ability to detect efficacy. Large and consistent clinical effects require smaller study numbers in comparison with placebo than an intervention with a less consistent effect. With appropriately large studies, small effects can be discerned statistically, but the clinical relevance of such therapy must be questioned. Regardless of whether the objective is to find out if a compound is effective at all or if efficacy can reach a certain threshold, the clinically relevant efficacy must be predetermined. This is a prerequisite for an adequate sample size calculation. The magnitude of efficacy—for example, nasal blockage changing 1 score step from moderate to mild—is easy to relate to an individual. The mean symptom score value of a population, however, is an abstract quantity, but can be translated to a clinically relevant quantity. The appreciation that a 0.5 mean score step improvement can be translated to, for example, an improvement of at least 1 score step in 50% of a population makes this easier to conceptualize. An alternative approach is to calculate the number needed to treat to achieve a particular outcome. Sadly, few clinical trials provide information in this format.

A special requirement for drug registration is to determine a lowest effective dose. A common scenario is that a drug has a defined dose response. Under the assumption of a sigmoidal dose-effect curve (Fig 2), any dose above the zero efficacy level can be found effective (statistically significant efficacy regardless of magnitude) given a large enough sample size. The discriminative capacity of the efficacy variable and the patient numbers will determine what magnitude of difference is statistically significant. The sample size must be driven by the magnitude of change seen as clinically relevant for the primary efficacy variable. Thus, there is relativity to the meaning of *effective*.

Fortunately, in rhinitis, there is guidance from established efficacious reference drugs. A difference between treatments in conventional clinical rhinitis trials of a 0.5 score step on a 0 to 9 scale (composite of blockage, secretion, and sneezing) can be detected with reasonable numbers of patients and has been considered a clinically relevant magnitude of efficacy.[12,13] The clinical relevance will of course depend on the starting reference symptom score, because a change from 1.0 to 0.5 might be considered a more relevant reduction than that from 8.0 to 7.5, even if both were statistically significant. Insufficient attention has been given to the magnitude of change in relationship to the baseline scores in the presentation of results. This aside, nasal corticosteroids can achieve superior efficacy by more than 2 score steps compared with placebo.[10]

A minimum of 2 doses with statistically significant difference in efficacy is necessary to make any clinical potency comparison between 2 drugs. This means the doses must be on the slope of the dose-effect curve (Fig 2, *example A*) to be able to demonstrate a dose dependency. If the doses compared are above the flat top end of the curve (Fig 2, *example B*), any doses could be chosen and would still be found not statistically different. Of course, "no statistical difference" between 2 medications cannot be interpreted as equal efficacy. To show equivalence, predetermined criteria for equality and a different statistical algorithm are necessary, usually demanding far bigger sample sizes.

Practical considerations

Time constraints typically apply to trials in rhinitis. If PAR is being studied, seasonal allergens or postseasonal hyperreactivity could influence the symptoms. It is necessary to time trials with a sufficient margin to avoid the major pollen season. In contrast, it is crucial to hit the season for SAR (Fig 1). The ambition is to include patients with comparable state of priming, duration of symptoms, and allergic inflammation. Start of treatment for all patients within a week or less, and within area region, is a way to make the disease under study more consistent. In multicenter studies, this may or may not be applicable depending on the geographic dispersion of the centers and the seasonal pattern of pollen exposure at those sites.

There is a risk of unfavorable weather conditions with low airborne concentrations of pollen. This will lead to lack of symptoms or very mild symptoms and reduce the

potential to demonstrate any efficacy. Including regions with reliable and predictable pollen seasons is thus preferable.

Preventive treatment is in principle different from a situation in which the start of treatment is driven by presence of symptoms. This distinction can be very delicate. Pollen forecasts and day-by-day monitoring of counts can help predict factors beyond human control to allow fine-tuning of time for start of treatment. To ensure that a symptomatic population is enrolled, minimum symptom criteria can be applied.

There are high demands on study management and logistics. Recruitment and enrollment of large numbers of patients within few days, at short notice, in a large number of geographically spread centers may be necessary. Scientific stringency must be weighed against practical feasibility. How far this compromise should be taken must be driven by the objectives. A very regulated and strict protocol with an effect on a patient's daily life can actually have an effect opposite the intended stringency. Recruitment will be difficult and will lead to a biased population sample, and there is a risk that lack of compliance will be concealed because of unwillingness to report divergence. As with most endeavors, experience and planning are key to success.

DISEASE MODELS OF ALLERGIC RHINITIS

One further step toward the study of efficacy of drugs in rhinitis is to standardize by controlling multiple factors, similar to a classical laboratory experiment.

Artificial seasonal models can achieve this, as in the nasal allergen challenge artificial season developed at Lund University, which is a daily repeat challenge model that produces low-grade symptoms.[14] In this setting, individual variation is minimized through a crossover design and by adjusting the challenge dose to the patient's reactivity through a challenge threshold procedure.

Nasal allergen provocation testing

Different techniques have been used to induce nasal responses in experimental challenge models. Allergens have been delivered by dripping,[19] pipettes,[20] or by paper discs.[21] Paper discs are helpful not only for challenge but also to enable the recovery of mucosal surface fluids and the measurement of solutes present in low concentrations, because of their absorptive properties,[21] but are potentially irritating and may induce exudative inflammation by themselves.[22] A disadvantage with these 3 methods is that they only challenge a localized area of the nasal mucosa. Nasal pump sprays containing allergen deliver the solution over a larger area of the nasal mucosa, mimicking the natural exposure of allergens to nasal mucosa. Nebulized pollen inhaled via the nose has also been used for nasal allergen challenge[23] and may give a better distribution of the allergens, but pump sprays are simpler. The allergens delivered by pump sprays or nebulizers are given in water-based formulations, in contrast with the solid form of natural allergen exposure. Dry powder, in the form of whole pollen grains, has also been applied topically to the nose[24] but results in an uneven distribution of the pollen. An additional technique is the nasal pool device, a compressible plastic container that can be loaded with challenge agents.[25] The patients can perform the challenges by themselves, and the fluid can be kept in contact with the nasal mucosa for a specific period. The nasal pool device method is easy to handle even in children.[26] However, a larger amount of allergen is needed to induce the allergic response, which increases the costs.

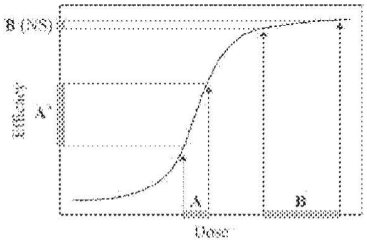

FIG 2. An imagined sigmoidal dose-efficacy curve illustrating the differences in efficacy between different doses at different parts of the curve: small dose difference and significant efficacy difference at the steep slope **(A)**, large dose difference and nonsignificant efficacy difference at the flat top end plateau **(B)**. *NS,* Nonsignificant.

Several kinds of allergens can be used. The most commonly used allergens are pollens delivered in the form of grains or extracts. The stability and purity of the extracts are crucial, however,[27] and extracts should be kept cool between challenges.

Acute allergen challenge model

A nasal challenge with appropriate allergen in a sensitized individual induces almost immediate nasal symptoms with itching, followed by sneezing watery discharge, and some minutes later by nasal congestion.[28] Acute provocation protocols, with measurement of acute symptoms and nasal lavage, provide insight into the acute disease process (see section on the objective monitoring of nasal airway inflammation). The acute provocations and corresponding responses are reproducible as long as enough time has elapsed between provocations. Because the nasal mucosal processes must return to a stable nonsymptomatic baseline, at least 7 days between provocations is recommended to minimize the priming effect[29] when symptoms are the main outcome. To achieve stable baseline symptoms between each provocation, the patients must be nonsymptomatic and out of their pollen season.

Similarly to nasal symptoms in natural allergic disease, an allergic individual's acute nasal response after 1 single allergen provocation depends on individual sensitivity and the amount of delivered pollen. Too high a dose of allergen may result in total nasal blockage, which limits the ability to perform nasal lavage in the absence of a decongestant. An allergen dose-response evaluation

is necessary either as the challenge protocol, or as a preliminary study to enable the selection of a single allergen concentration for administration. The administration of a nasal decongestant limits the ability to monitor indices of nasal patency and should be avoided if this is an outcome variable of importance. The titration of the allergen challenge concentration to achieve a predetermined ballpark response is important in pharmacologic intervention studies, because if the given response is too strong, any pharmacologic treatment effect may not be discerned. Correspondingly, if the response is too weak, it may be difficult to identify real therapeutic effects.

Predictive value of the acute nasal allergen challenge model

The acute response depends on mast cell degranulation with mediator release and the end-organ responses. The H_1-antihistamines modify the acute challenge response and have a profile similar to that described in naturally occurring disease, with some differences in magnitude. The effect of H_1-antihistamines in the challenge model on nasal itching and sneezing is greater than that seen in naturally occurring disease.[30] Surprisingly, hardly any published studies exist regarding the effects of leukotriene receptor antagonists (LTRAs) on the acute nasal allergen challenge model, despite several studies being undertaken with such a challenge model within the lower airways.[31] Although corticosteroids administered immediately before nasal allergen challenge have no effect, pretreatment with topical corticosteroids for a week reduces the acute nasal symptom response by about 50%.[32,33] This effect of intranasal steroid therapy has been attributed to depletion of the epithelial/superficial mucosal mast cell population with continued therapy. Consistent with this, 2-week treatment with intranasal mometasone has been shown to reduce the nasal response to AMP, a mast cell secretagogue, but to have no effect on nasal histamine challenge.[34] With AMP challenge, both the antihistamine fexofenadine and the LTRA montelukast modify the nasal obstructive response, consistent with the release of both histamine and sulfidopeptide leukotrienes with this stimulus.[35] Although the outcome measures were different in the studies investigating the receptor antagonists and the intranasal steroid intervention with AMP challenge, the magnitude of the response with the intranasal steroid was more substantial, consistent with the clinical differences between these different modes of therapy. However, both the nasal allergen and, in particular, the AMP challenge are mast cell-dependent models, and not all results with single-dose pretreatment translate to multiple-dose treatment in clinical disease.[36,37] It also seems difficult to assess any potency differences between nasal corticosteroids in acute challenge protocols. It could be that nasal mucosal inflammatory changes induced in chronic allergic inflammation are not reproduced by acute challenge protocols. In other words, the well-known clinical efficacy of topical corticosteroid therapy is not as clearly demonstrable in acute provocation protocols as in real allergic life.

Predictive value of the nasal late-phase response to allergen challenge

A second phase of bronchial obstruction after allergen inhalation in allergic asthma has been termed the *late-phase response*.[38] This late-phase response, which occurs in many subjects with asthma,[39] is considered a reflection of the type of airway inflammation that occurs in naturally occurring disease.

However, the nose is different from the lower airways in that all of the allergen is delivered to nasal mucosa with aerosol application, whereas with inhalation allergen challenge, only 10% to 15% of the aerosolized dose reaches the lower airways, and it is spread over a much larger surface area. As such, the local concentration of allergen per unit area of the nose is likely to be considerably higher than that within the lower airways, and the response is thus different. This may explain why no clearly defined early and late obstructive response is evident within the nose. Instead, there is a protracted obstructive response within the upper airway, as if the late response merges with the immediate response to produce a continuous phenomenon that may take several hours to subside.[40] The obstructive effect in the nose is vascular, whereas that in the lower airway is dominated by smooth muscle constriction. There is, however, a biphasic cellular response in the nose with later accumulation of eosinophils and basophils. These cells do not have any clinical consequences, in that there is no consistent late nasal itch, sneeze, or discharge response. Although small symptomatic changes have been described in some studies in selected individuals, this is far from a consistent finding.[32,40-43] This cellular late-phase nasal response is similar to the lower airway late-phase and is sensitive to the inhibitory effects of corticosteroids.[32,42,44] The so-called *nasal late-phase response*, however, is a poorly defined period from somewhere between a few hours after the acute reaction as long as 24 to 48 hours later. The ongoing inflammatory reaction in the nasal mucosa can be identified by increased mucosal output of inflammatory markers, ongoing plasma exudation, signs of local cell activation on the mucosal surface,[45] and increased mucosal output of cytokines,[46] and is sensitive to anti-inflammatory treatment.[46,47] Both oral and topical glucocorticosteroids (GCS) have been demonstrated to reduce late-phase inflammatory responses.[32,42] However, the relevance of the effects of anti-inflammatory drugs on the late-phase cellular response as a predictor of the drug effect in allergic rhinitis is uncertain, because most studies have been performed with steroids that intervene at multiple junctions in the process and thus influence many cellular pathways.

Relevance of repeated challenge responses

Connell[48] first described increased responsiveness of the nose after daily repeated allergen provocations, in which individuals with allergy develop a stronger response to the same pollen dose when exposed to that dose for several days, termed a *priming phenomenon*. This priming phenomenon, in contrast with the acute response,

is reproducible and very sensitive to topical corticosteroids.[32,33,49] Whether the priming phenomenon or allergen-induced hyperreactivity can be used for assessment of dose-response efficacy of corticosteroids or to compare the potency between different corticosteroids is unknown.

Chamber studies

Exposure chambers have been developed to reduce some negative features of clinical pollen studies, like the unpredictable levels of pollen, and weather conditions during the study period. Exposure chambers now also ensure even distribution of the pollen to the participants in the chamber, whereas early chambers did not do so.[50] Horak and Jager[51] first described the Vienna Chamber, in which as many as 7 patients could be exposed for several hours under controlled conditions at the same time. Other exposure chambers now can expose as many as 160 patients at the same time, which makes chamber provocations very convenient once the patients have been recruited.[52]

The exposure chamber delivers a controlled pollen exposure over a certain period and allows assessment of responses at any time point throughout the challenge process. Air flows into the room at a certain rate, and pollens are introduced into the ventilation system. Fans are then arranged throughout the room so that the allergens are evenly distributed, and, at the same time, the pollen levels in the room can be measured continuously. Hence, the amount of pollens can be controlled and adjusted to provide a similar density of exposure as in the ambient air during natural peak pollen days, reproducing many of the study conditions of an outdoor allergy study. Different allergens can be given in the chambers, like house dust mite[53] and cat allergens,[54,55] but the most commonly used allergens are pollens.[55] Onset of allergic symptoms has been investigated in the chambers, and the efficacy of different antiallergic treatments has been investigated. The chamber provocations seem especially useful for studies to evaluate the onset time of antiallergic drugs.[56,57] Antihistamines can reduce nasal symptoms within 1 to 1.5 hours after intake of the drug compared with placebo in the exposure chamber.[56] Topical triamcinolone reduced nasal symptoms 10 hours after spraying,[56] and nasal symptoms were reduced 7 hours after topical budesonide.[57] An even earlier effect was evident 3 hours after budesonide administration when nasal obstruction was measured objectively (nasal peak flow meter) rather than subjectively by symptoms reporting.

Park studies

In park studies, patients are exposed to natural pollen under natural but controlled settings. Park studies have the advantage that the interindividual variability of the pollen exposure can be minimized. The exposure time can be well controlled, and the patients can be monitored very often and at regular intervals over the whole day. Park studies were first described by Connell[58] and have been used since then predominantly with therapies such as antihistamines, which would be expected to have a rapid onset of effect. The major limitation is that in park studies, patients can be observed only over 1 day, so longer observation periods as in natural pollen disease cannot be performed. The weather pattern and the natural pollen exposure cannot be guaranteed. Furthermore, it is time-consuming to organize a park study, but subjects can be monitored closely, and food intake can be standardized. The subjects should be in close vicinity to the locations where the pollen traps are situated so that the exposure of relevance can be measured. Park studies have also been performed in multiple centers,[59] and in contrast with exposure chambers, parks can be found in almost any city. Similar to chamber studies, patients can assess their symptoms at regular times over a whole day. Onset time for antihistamines has been demonstrated to occur within 2 hours after dosing. This onset time is similar to the onset time for antihistamines in chamber studies.[59-61] Dose-response relationships with new therapies may sometimes be difficult to interpret.[62]

Repeated pollen exposure

Daily repeated pollen provocations over a week, under well-controlled conditions, have been shown to induce similar inflammatory changes and symptoms, as can be seen in natural disease.[63] These changes can also be reduced by topical corticosteroids to a similar extent as in the natural pollen season. Repeated daily provocations can be performed outside the pollen season, and when a crossover design is used, the number of participating patients can be reduced. Repeated pollen provocations were described initially by Blackley as long ago as 1873[64] and have since been performed to observe and understand cellular and pathophysiological changes without the variability of the onset of the pollen season and the weather conditions, which are important drawbacks in natural pollen disease studies.[65-67] Some features of the natural allergic disease may not be well studied, because the repeated provocations have not been given for longer than 2 weeks (because of practical considerations). Furthermore, the daily repeated challenges have been undertaken with soluble allergens, which, as with single or repeat challenge provocations, are not the true type of pollens that patients are exposed to in real life. Whether challenges with aqueous solutions do elicit a different unnatural response not seen in natural pollen disease is not known. However, this model has been able to provide valid data with respect to nasal corticosteroids.

In a repeated allergen challenge model, in which once-daily repeated individualized pollen challenges were performed over 8 days, it was possible to assess a dose-response relationship for intranasal steroids.[14] The individual dose of allergen was titrated to elicit only moderate nasal symptoms and was then administered once every morning over the whole challenge period. At the end of the week when symptoms were stable, a dose-response effect of the topical corticosteroid budesonide was seen, because budesonide 256 μg/d was superior to 64 μg/d.[14] The same artificial pollen season has also been used to evaluate and compare equipotent dose effects with other

currently available or potential topical corticosteroids.[15,16] Interestingly, the placebo curves for nasal symptoms for the last 3 days in each artificial pollen season have an almost identical appearance in 3 different studies (with different patients and in 3 consecutive winter seasons), indicating that the artificial pollen season is a very stable and reproducible method.[14-16]

ASSESSMENT OF RHINITIS IN THE PEDIATRIC PATIENT

Rhinitis is a frequent cause of morbidity in children, affecting as many as 40% of children in the United States and 20% of children worldwide.[1,68,69] In adulthood, the sex ratio is approximately equal, whereas in childhood, males outnumber females.[70,71] First-born children are at a higher risk for allergic rhinitis, as are children with early introduction of food or formula feeds. Other risk factors include heavy maternal cigarette smoking in the first year of life, exposure to indoor allergens including animals or dust mites, serum IgE levels >100 IU/mL before age 6 years, and a family history of atopy.[72] It is now appreciated that there may not be a linear relationship between allergen exposure and the subsequent expression of sensitization or allergic disease expression.[73]

The effect of allergic rhinitis on children is substantial, yet parents and physicians are often unaware of the scope of its symptoms.[74] Nasal symptoms (eg, rhinorrhea, nasal congestion, sneezing, and itching of the nose), associated symptoms (eg, headache and fatigue), and side effects of treatment can all have pronounced effects on quality of life in children with rhinitis that differ from those in adults.[75,76] Adolescents frequently report nasal and ocular symptoms, with associated thirst, headache, fatigue, and irritability.[75] Other difficulties include poor concentration and an inability to do school work effectively, in addition to limitations in outside activities.[75] Children aged 6 to 12 years with rhinitis tend to be bothered by nasal, ocular, and systemic symptoms, but less by emotional problems and activity limitations.[77]

In addition to the >2 million school days lost annually in the United States because of rhinitis,[70] impaired learning in children[78,79] and cognitive difficulties (slower cognitive processing and difficulties in working memory) are associated with symptoms of allergic rhinitis, suggesting an effect of the disease on school performance.[80] Additional studies demonstrate a greater reduction in learning ability in children with rhinitis who are treated with diphenhydramine, a sedating antihistamine,[78,79] suggesting that some treatments may further compromise school performance.

Associations with rhinitis

Extensive epidemiologic, clinical, and laboratory studies demonstrate a link between rhinitis and asthma.[1] Both allergic rhinitis and allergic asthma are IgE-mediated diseases that are triggered by many of the same allergens (eg, grass, dust mites, cat dander). The incidence of allergic rhinitis and asthma in atopic children varies but has been estimated to be 50% to 60%.[81] Epidemiologic studies show that rhinitis and asthma frequently coexist, with asthma diagnosed in as many as 58% of patients with rhinitis and rhinitis diagnosed in as many as 78% of patients with asthma.[74] The combination of allergic rhinitis and asthma is the most frequently reported disease combination in persons younger than 18 years.[82] The presence of bronchial hyperresponsiveness has been well established in patients with allergic rhinitis and no symptoms of clinical asthma. In one study, 73 of 197 patients with seasonal rhinitis during allergy season and 128 of 192 patients with perennial rhinitis were documented with bronchial hyperresponsiveness.[83] Increased bronchial hyperresponsiveness generally precedes the development of asthma and may be a risk factor for developing asthma.[84,85]

Sinusitis and otitis media are common in children with allergic rhinitis. The association between rhinitis and sinusitis is supported by a high incidence of atopy in children with chronic sinusitis.[86,87] Abnormal sinus radiographs have been reported in children with allergic rhinitis; in some studies, as many as 70% of children with allergy and chronic rhinitis have abnormal findings on sinus radiograph studies.[88] Common pathophysiologic features of rhinitis and sinusitis include decreased mucociliary clearance, tissue edema, and increased mucous production.[74]

Approximately 35% of children with recurrent otitis media with effusion (OME) have allergic rhinitis.[89] These epidemiologic links, as well as a greater susceptibility of atopic children in general to both acute otitis media and chronic OME, suggest that IgE-mediated allergies may be involved in the pathogenesis of OME. The findings of histamine and other inflammatory mediators in middle ear effusions of children with OME support this pathogenesis, although this is not an invariable finding. Otitis media and OME can thus result from nasal inflammation because of allergy, causing subsequent obstruction, fluid accumulation, and bacterial infection,[90] although other factors such as viral infection are also causes of OME.

Children with rhinitis are mouth breathers and are at risk for abnormal facial development, with lengthened facial features (including a narrower maxillary arch, greater palatal height, and greater anterior facial height). They also have a higher prevalence of posterior dental cross bite compared with controls without allergy.[91,92]

Diagnosis of rhinitis in children

Diagnostic features of pediatric and adult rhinitis are very similar; however, differences do exist. The differential diagnosis of allergic rhinitis in children, shown in Table I, includes diagnoses that are particularly relevant to the pediatric population.[70] Facial features and mannerisms characteristic of pediatric allergic rhinitis that may help to identify rhinitis in children include the allergic salute, allergic crease, allergic shiner, and Dennie Morgan lines.[93]

Accurate diagnosis of rhinitis depends on a comprehensive history and thorough physical examination with supplemental laboratory tests. A comprehensive history should contain information pertaining to (1) symptoms onset (ie, infancy vs childhood, after viral upper respiratory infection, trauma, or acquisition of a new pet or home); (2) frequency, duration, seasonality, and severity of symptoms; (3) character and color of secretions; (4) precipitating (eg, allergens, climate conditions) and associated (eg, atopic disorders or infection) factors; and (5) previous treatment/medication responses.[70]

Because otitis media and OME are frequent pediatric complications of rhinitis, physical examination should include the ears (evaluating for infection, fluid, eustachian tube dysfunction, with additional use of a pneumatic otoscope or impedance tympanometer).[94] In addition, the nasal pharynx should be examined for evidence of tonsillar and adenoid hypertrophy, and the chest for asthma or bronchitis.[94]

The laboratory work-up for children with rhinitis is similar to that for adults and includes allergy testing for potential food allergens, seasonal allergens, and perennial inhalant allergens. Allergy testing for seasonal allergens can be performed in children who are at least 2 years of age but is commonly not done before 5 years of age.[95,96] Testing for potential food allergens can be performed in children younger than 5 years when indicated. When interpreting the results of skin prick tests in pediatric rhinitis, it is important to realize that positive allergen-induced tests generate smaller wheals in infants and young children than in older children and adults[97] because of lower specific-IgE levels and reduced skin reactivity, especially in infants. Use of a multihead puncture device may facilitate testing in uncooperative infants and young children.[70]

Other tests that may be indicated on a case-by-case basis include nasal cytology (to help differentiate allergic rhinitis and nonallergic, noninfectious rhinitis with eosinophilia from other forms of rhinitis) and specific diagnostic tests performed to rule out alternate diagnoses (eg, sweat test for suspected cystic fibrosis). In children with suspected sinus disease, computerized tomography (CT) scans are more sensitive than standard radiographs.[70] Total serum IgE levels should not be routinely determined in children with allergic rhinitis because they may have low levels of serum IgE (<50 IU/mL) despite a significantly positive skin test and correlating history.[94]

Treatment trials of allergic rhinitis in children

The considerations relating to trial design and the conduct of clinical trials in children are essentially the same as in adults, although specific endpoints are of relevance to children. As such, specific quality-of-life questionnaires have been developed for children of different ages to focus on the different effects of rhinitis and associated conditions in different age groups, and monitoring of growth is a specific issue in relationship to intranasal steroid therapy in children (see section on clinical outcome measures and adverse effect monitoring in rhinitis).

TABLE I. Differential diagnosis of pediatric allergic rhinitis

Viral rhinitis: average of 6 episodes per year in children 2-6 y old
Foreign body: typically presents as unilateral purulent rhinorrhea
Food allergy: nasal and ocular symptoms occur during 30% of allergic reactions to food
Pharyngonasal reflux: results from prematurity, cleft palate, neuromuscular disease
Nasal obstruction: structural defects or adenoid hypertrophy
Nonallergic, noninfectious rhinitis with eosinophilia and nasal polyps: rarely diagnosed in children

An important aspect of any pharmacologic treatment is patient compliance. Steps that can be taken to increase medication compliance and ensure optimal therapeutic benefit in children with rhinitis include the use of aqueous versus aerosol formulations and liquid formulations versus tablets/capsules, when available. Sprays with smaller nasal applicators also should be selected for pediatric patients. Adequate instruction on the proper use of devices is also critical and should be provided in a way that children can easily understand.

NASAL ASSESSMENT IN NASAL POLYPOSIS

Nasal polyps are fluid-filled sacks formed in the upper part of the nasal cavity[98] consisting of protrusions of nasal mucosa with a loose connective tissue with a characteristic eosinophilic infiltration, similar to that of bronchial asthma.[99] This represents an inflammation of the nose and the sinuses, rhinosinusitis, the initial treatment of which is medical,[100-102] whereas surgery is used when such intervention is inadequate to control the disease.[103-105]

Corticosteroids administered either intranasally or orally have the best evidence for use in the management of nasal polyposis, whereas little has been published on drug types frequently used in other types of rhinitis, such as antihistamines or cromoglycate.[106,107] Consequently, experience from clinical research using corticosteroids is the main basis for the understanding of the value of outcome measures in the evaluation of drug intervention in nasal polyposis, although other trials, such as those evaluating antifungal therapy, have also been instructive.[108] Outcome measures vary and may relate to patient symptom reporting, the subjective and objective scoring of polyp size and extent, the need for additional medication such as oral steroids, evaluation of the effect of polyps on nasal airflow, sense of smell and mucociliary clearance, and evaluation of markers of nasal mucosal inflammation.[108-110] Such outcome evaluation suggests that intranasal steroids with low systemic bioavailability, although they improve nasal polyposis, may be insufficient as a sole therapy to prevent recurrence in those in whom the disease was sufficiently severe to necessitate surgery.[109,110] The reported beneficial effects on recurrence rate in open studies with some other steroids could

relate to differences in the severity of the underlying disease being treated but may also relate to a systemic effect, with such therapy contributing to their efficacy.[111] This notion is supported by the open observation that depot steroid injection in conjunction with surgery improves the sense of smell.[112]

Confounding factors for nasal polyp assessments

Nasal polyps may be part of several different underlying disease processes. The association with asthma is most common[113] and may be linked to aspirin sensitivity. In general, the prognosis for a good treatment outcome is poorer the more clinically manifest are the associated diseases, as seen in the triad of asthma, aspirin intolerance, and nasal polyps.[114] Objective monitoring of the outcome after endoscopic sinus surgery has identified that both the extent of the sinus disease and a history of previous sinus surgery are factors associated with a poorer long-term outcome.[115] CT scanning did not appear to be a positive predictor in this study for either the extent of surgery or the healing outcome. CT scans of the sinuses show partial or total occlusion of the sinuses by soft tissue in many patients.[116] No reports of controlled studies documenting efficacy of antibiotic treatment exist, although there is considerable interest in the role of infections, such as *Staphylococcus aureus*, in driving the formation of polyps, as a result of IgE directed against their enterotoxins.[117-119]

Significant treatment efficacy

The pathogenesis of nasal polyps is incompletely understood, and at present, treatment is symptomatic. The most important judge of efficacy is the patient, who consults the physician to relieve symptoms. Basically, this should be supported by objective documentation of efficacy by randomized and controlled studies.[120] Unfortunately, this is weakened because the interindividual variation discussed diffuses the ideal covariation between objective measures. Some indicators of patient satisfaction are the use of rescue medication and the surgical procedures required. Accordingly, treatment efficacy is estimated by combining the patient's opinion, including appropriate indicators and the results of the various objective measures. This requires that improvement is statistically significant but also clinically relevant, which is only vaguely defined. In most cases, statistically significant improvements in objective measures are associated with patient satisfaction. In general, statistically significant improvement denotes clinical relevance, but whether the patients are satisfied is still highly subjective.

Outcome measurements in nasal polyp assessment

Outcome measurements in nasal polyp assessment will be rated below for ease of performance and repeatability in the ear, nose, and throat (ENT) department (0 = difficult to +++ = easy), based on the personal experience of the author and the literature.[121-123]

Considerable sources of variation are apparent from comparison of the results from seemingly similar studies. In addition, as discussed in the clinical trial design section, placebo-controlled studies consistently show placebo efficacy. The basis for such effects in nasal polyposis has been little investigated.

Diaries

Ease of performance (+++). Patients' structured notes of symptom scores, treatment satisfaction, and use of escape medication. Initially as daily recordings, and weekly or monthly during the later phases of long-term follow-up.

Repeatability (+++). Detailed information may be obtained that correlates well with objective measures. Provided the layout and contents of the diaries have been well composed, this requires good patient discipline and compliance. This may be facilitated by motivation and involvement via appropriate information delivered at all levels of the study organization.

Nasal endoscopy

Ease of performance (+++). Nasal endoscopy can exclude anatomical deformities and to categorize the size of polyps according to various scoring systems.[124] The use of flexible or rigid endoscopes means that this is part of specialist routine, which also includes the sampling of a biopsy or cytology specimen.

Repeatability (++). Despite the advanced technical equipment available, the scoring system for endoscopy is simple and the results are subjective, influenced by the experience of the investigator. Nevertheless, the 4-category system relating the size of the polyps to the inferior turbinate provides stable results that vary simultaneously with other measures and appear more sensitive than the patient's subjective evaluation of their degree of nasal obstruction.[124-126]

Nasal peak flow

Ease of performance (++). This measure was developed for monitoring lung function but has similar qualities for measuring relative changes in nasal passage.[127-130] Because the driving force originates from the lungs, this is supposed to be constant.[131] In case of suspected or documented concurrent changes,[132] this may be compensated by recording the nasal peak flow index—that is, nasal peak flow/oral peak flow.[133] This may be relevant in nasal polyposis because many patients show abnormal bronchial reactivity or clinically express asthma. In contrast with measurement during expiration, hygienic concerns related to secretions being blown into the equipment during expiration have led to the development of a reverse system for measurement of NPIF.[134,135] However, collapsing of the distal nose during the inspiration may hamper the results in some patients.

Repeatability (+++). The correct technique must be learned from instruction, which in most patients takes 5 to 10 minutes. In general, clinic measurement has been used

for monitoring in nasal polyps rather than home monitoring, although home monitoring has a good track record in other disease areas such as asthma.[136] The most important source of variation is the occurrence of upper respiratory infections influencing both lung function and nasal passage. Because of overlapping symptomatology with nasal polyps, it may be difficult to define the time of onset and resolution. In addition, infection may worsen preexisting asthma and thereby modify NPIF independent of any nasal effects.

Sense of smell

Ease of performance (++). Increasing evidence indicates that decreased or absent sense of smell has a major influence on a patient's quality of life.[137] The measurement of smell discrimination—that is, the ability to distinguish between different odors at suprathreshold concentrations—has been developed and validated in various systems such as the University of Pennsylvania Smell Identification Test[138] (see section on clinical outcome measures). The corresponding measurement of smell thresholds—that is, the ability to measure the lowest concentration at which an odor can be sensed or identified—is difficult for clinical use.[139] In principle, it is similar to a hearing test by an audiometer, in which the test stimulus can be precisely delivered. This is very complicated for the smell stimulus, and the corresponding equipment (olfactometer) is only available in specialized laboratories.[140,141] Simpler systems for clinical use have been developed, but their precision is difficult to assess.[142,143] Unfortunately, this is relevant for the evaluation of treatment efficacy in nasal polyposis because nasal polyps may block the passage to the olfactory area and cause elevation or absence of thresholds, whereas little is known of their influence on discrimination.[144] For the evaluation of nasal polyps, it is not known whether sensitivity of the systems for semiquantitative threshold measurement is favorable compared with a patient's subjective reporting. It seems that the most sensitive measure so far is the patient's scoring of smell ability in diaries.

Repeatability (+). Despite its importance to the patient, changes in the ability to smell are difficult to record satisfactorily. Furthermore, the considerable variations in such measures seem to exceed those of other variables. This may be a result of the anatomy of the olfactory system, in which both the degree and localization of mucosal swelling/nasal polyps influence quantitation.[145] In general, sense of smell varies with changes in nasal obstruction.

Quality of life estimates

Ease of measurement (+). Recent developments of questionnaires and appropriate validation of both general and disease-specific variants have shown major effect from nasal polyps on quality of life. Generic questionnaires such as the Medical Outcomes Survey Short Form 36 (SF-36) and the more specific Sinonasal Outcome Test–20 have been used.[108,109,146,147] Improvement has been associated with both medical and surgical treatment.[109,146]

Repeatability. No data are available.

Nasal lavage

Ease of measurement (0 to +). Fluid from nasal washing may be analyzed for biochemical markers reflecting the degree and type of inflammation present.[148] This has been incorporated in some clinical trials for monitoring treatment efficacy (see section on nasal inflammation assessment).[108,147,149]

Repeatability. No data are available.

CT scanning

Ease of measurement (0 to +). Resources and x-ray exposure may be minimized by using special protocols that calculate the volume of soft tissue in the sinuses and the nasal cavity.[150] Only a weak correlation has been reported between the CT scan score and either the symptom severity score or the endoscopic evaluation of severity.[147] Variations in volume seem to correlate poorly with those of other measures, and some sources of error, such as secretions, are difficult to control for.[151,152] However, CT scanning has been used as the primary outcome measure in some studies.[108]

Repeatability. No data are available.

Acoustic rhinometry

Ease of measurement (0 to +). Nasal cavity volume may be measured, and variations in the decongested nose will reflect changes in nasal polyp size.[153,154]

Repeatability. No data are available.

Measurement of patient satisfaction

Measuring patient satisfaction may be the focus in future clinical research, and suitable techniques are being developed. This is achieved by condensing and refining the cumbersome procedures for interview and questionnaire investigation—that is, separating estimates of quality of life into global and disease-specific qualities. With further validation and development, patient satisfaction measures are applicable to busy clinicians and may become superior measures of drug intervention in nasal polyposis. Outcomes such as the sinonasal outcome test–20 have been used and have been shown to provide valid information.[109]

PHARMACOLOGIC INTERVENTION IN CLINICAL TRIALS

The 2 major classes of drug used in the treatment of rhinitis are corticosteroids and antihistamines, which can be administered locally and systemically. LTRA, vasoconstrictors, and anticholinergics play a smaller role. This section is divided into (1) general considerations, (2) factors leading to variability, and (3) a review of the different nasal outcomes for each drug class.

General considerations

Local versus systemic drug administration. Rhinitis is a disease confined to a small organ, about 0.1% of the

total body mass. Reaching this small amount of diseased tissue by local treatment is, in principle, preferable to systemic treatment, which reaches about 70 kg of completely normal tissue. The correctness of this principle was illustrated some years ago when it was realized that the oral antihistamines terfenadine and astemizole can induce serious cardiac adverse events and even deaths when administered with therapy that modifies their metabolism, eg, ketokonazole.[155]

Advantages of local drug administration

CORTICOSTEROIDS. The side effects of systemic corticosteroids are well known. There is overwhelming evidence from a substantial number of placebo-controlled studies that nasal corticosteroid treatment is highly effective and very safe in the treatment of allergic rhinitis.[1,4,156,157] Although controlled-drug comparative studies are few, they have indicated that local treatment is at least as effective as systemic low-dose treatment.[158]

ANTIHISTAMINES. Several comparative studies have shown that local treatment with an antihistamine is at least as effective as oral treatment.[159-162] A quicker onset of action is an advantage of local treatment.[163] This is a definite advantage in the eye, where the relief is obtained within minutes. It takes 1 hour for an oral preparation to work.[163] Within this period, a patient with itchy eyes cannot avoid rubbing the eyes, causing further irritation and redness. In addition, local treatment is completely devoid of systemic side effects.

VASOCONSTRICTORS. The effect of a local vasoconstrictor starts within minutes, whereas it takes 1 hour before an oral compound is effective. The decongestant effect is more pronounced with a nasal vasoconstrictor than with a tablet.[164] In addition, an oral vasoconstrictor, acting on all blood vessels in the body, has a low therapeutic index with regard to systemic side effects, and there are several contraindications to oral treatment.[164]

ANTICHOLINERGIC DRUGS. When watery rhinorrhea is a major problem, intranasal ipratropium bromide can significantly reduce this symptom.[165] Systemic use of this type of medication will cause intolerable side effects, such as mouth dryness,[165] and for this reason, systemic anticholinergics are not used for the treatment of rhinorrhea.

Disadvantages of local drug administration

INTRANASAL DRUG DISTRIBUTION. Studies have shown that the intranasal distribution of a locally administered drug is not optimal. Only 20% of a pressurized aerosol and 50% of an aqueous spray will reach the target, the ciliated mucous membrane.[166] In addition, there is no reason to believe that intranasal medication will reach the ostiomeatal complex, which is the origin of nasal polyps and of decisive importance for the development of pathology in the paranasal sinuses.

IRRITANCY FROM ADDED PRESERVATIVES. It is necessary to add a preservative to an aqueous nasal spray. The preservative can cause some immediate nasal irritation, which is in part a sign of the rhinitis-induced hyperresponsiveness, and will diminish with time when an intranasal corticosteroid is used.[167] However, the commonly used antimicrobial preservative benzalkonium chloride can add to nasal hyperresponsiveness.[168] It is cytotoxic, and *in vitro* studies have clearly shown that it damages cilia and impairs mucociliary transport.[168] However, not all studies have shown this adverse effect to be of clinical significance.[169]

LOCAL SIDE EFFECTS. Intranasal corticosteroids frequently cause blood-tinged nasal secretions, occasionally nose bleeding, and in the rare case, a septal perforation.[170] Prolonged use of an intranasal vasoconstrictor causes rhinitis medicamentosa. The use of intranasal ipratropium bromide can cause a sensation of nasal dryness.[170]

Effect on nasal inflammation

It is a generally accepted concept that rhinitis is an inflammatory disease of the nasal mucosa and that inflammation is the basic cause of the nasal symptoms.[1,4,171]

CORTICOSTEROIDS. Corticosteroids have a broad anti-inflammatory activity and are often considered to be effective in all types of rhinitis, but that is not correct. Although corticosteroids are highly effective in allergic rhinitis, they have little or no effect in the common cold.[172] It seems that corticosteroid treatment is effective when the inflammation is eosinophil-dominated but not when it is neutrophil-dominated. Nonallergic, noninfectious rhinitis is a disease of unknown etiology (idiopathic rhinitis), and many but not all of these patients will respond to corticosteroids.[156] It is believed but not proven that corticosteroid responsiveness in these patients parallels the occurrence of eosinophils in a nasal smear.

ANTIHISTAMINES. A series of studies has shown that the second-generation antihistamines possess a series of anti-inflammatory effects in addition to their antagonism of histamine at the H_1-receptor.[173] To make any particular antihistamine stand out therapeutically or commercially from the other, it is often claimed that these experimental findings are of clinical importance. Such claims with the second-generation antihistamines should indeed be considered within the clinical sphere, and clear added benefit should be evident in relationship to symptomatic outcome measures if such purported anti-inflammatory activity is of relevance. It has been argued that if these claims were clinically relevant, the second-generation antihistamines should be effective on nasal blockage, measured by objective tests, in improving sense of smell, in modifying nasal hyperresponsiveness, in inhibiting the late-phase nasal response to allergen challenge, in reducing nasal metachromatic cellular inflammation, and in improving nasal polyposis. These are all effects that might be anticipated from a nasal steroid. However, it is unrealistic to anticipate such a broad profile of effect, and indeed, if H_1-antihistamines had such properties, they would be anticipated to be clinically as effective as an intranasal steroid, which they are not. This does not mean, however, that such drugs do not modify to a lesser extent some selective aspects of the inflammatory process. Some have been shown to modify, in some but not all studies, the

nasal eosinophil recruitment.[174-176] However, such action is now appreciated to be largely irrelevant as far as symptomatic clinical disease expression is concerned in allergic rhinitis. Eosinophils are a marker of the allergic inflammatory process, but there is no relationship between subjects in the extent of eosinophilic inflammation, or indeed the extent of eosinophil activation, and the severity of symptom expression. However, several newer H_1-antihistamines have been identified as having an effect in modifying, to a small extent, nasal obstruction, and this clinical benefit could indeed relate to an additional clinically relevant anti-inflammatory effect over and above pure H_1-receptor antagonism. Such effects are at present small and are insufficient to categorize such therapies as a distinct therapeutic group. These considerations are also compounded by the appreciation that some receptor antagonists per se may have additional properties if acting as an inverse agonist rather than as a simple neutral antagonist. The receptor antagonists in both these circumstances will antagonize the exogenous effects of receptor stimulation by an agonist, but the inverse agonist may potentially have additional activities linked to its binding to the H_1-receptor. Suffice it to say that at present, it is most appropriate to consider second-generation antihistamines as H_1-antihistamines in the treatment of symptomatic rhinitis. Two consistent observations are in favor of this statement. First, controlled clinical studies have uniformly shown intranasal corticosteroids to be more effective on all nasal symptoms, in particular nasal blockage, than antihistamines.[177,178] Second, companies claiming anti-inflammatory effects of their antihistamine have often added an oral vasoconstrictor to the antihistamine, which improves the efficacy on nasal blockage.[179-181] This addition is a reflection of the lack of effect of the antihistamine as a sole therapy.

LEUKOTRIENE RECEPTOR ANTAGONISTS. The effect of leukotriene receptor antagonism is discussed below in the section relating to these agents.

Factors leading to variability of drug efficacy

Sneezing, discharge, and congestion. When intranasal medication is used in a sneezing nose, a runny nose, or a blocked nose, it is reasonable to assume that the drug may not reach all nasal receptors and that the efficacy of the treatment is therefore reduced. This issue has not been sufficiently addressed in controlled clinical studies. A single study has shown that rhinorrhea does not reduce the efficacy of the local antihistamine levocabastine.[182] Obviously, intranasal medication cannot be given in a completely blocked nose or nostril, but its effect in a partially blocked nose has not been investigated. One study has shown that pretreatment with a systemic corticosteroid, which will open a blocked nose, can significantly increase the subsequent response to an intranasal corticosteroid in perennial rhinitis.[183]

Patient compliance. When a patient has symptoms in the eyes, the nose, and perhaps the skin, it is easier to treat all symptoms with a single medication. In such patients, oral treatment may therefore have a better patient compliance than local treatment of each diseased organ. The high sales figures of oral antihistamines support this statement. However, the marked differences in the use of oral and of local treatment between countries indicates that the doctor's opinion and recommendation is important for the patient's choice of therapy. Probably, information on the advantages of local treatment will increase the compliance and the usage of this type of therapy.

Specific medications and nasal assessment

Intranasal corticosteroids

NASAL SYMPTOMS. In allergic rhinitis, intranasal corticosteroids have a marked effect on nasal itching, sneezing, rhinorrhea, and nasal blockage. In clinical trials, recording of symptoms usually uses a simple score system (–, +, ++, +++). Apparently, this gives the same distinction between active and placebo treatment as a more detailed symptom recording (hours per day with symptoms, number of sneezes and of nose blowing).[184] However, the latter offers a better characteristic of the severity of the disease in the individual patient. In addition, improvement in one symptom (eg, sneezing) may have an influence on another symptom (eg, blockage) when an ordinary diary card is completed in the evening. This may offer a potential explanation for why antihistamines have some effect on blockage scores and why intranasal corticosteroids, in several studies, appear to have an effect on eye symptoms.[177,178] However, alternative pharmacologic explanations are more likely to account for these findings.

ONSET AND DURATION OF ACTION. The effect on nasal symptoms can already be detected 3 hours after start of medication.[57] The effect will reach a maximum level after a few days in seasonal rhinitis[185] and after a few weeks in perennial rhinitis and nasal polyposis.[186] Although this anti-inflammatory treatment has a longer lasting effect than antihistamines,[187] there are no data to suggest a disease-modifying effect in rhinitis,[187] in contrast with inhaled corticosteroid in asthma.[188] Intranasal corticosteroid treatment can inhibit the seasonal increase in specific IgE antibodies in the blood,[189] but the clinical significance of this observation remains unclear.

OLFACTION. A reduced sense of smell is an annoying symptom for many patients, especially patients with nasal polyps, and it is rarely recorded as an outcome measure in clinical trials. Although some studies have indicated a moderate effect of intranasal corticosteroids in perennial rhinitis, the effect in nasal polyposis is marginal.[190]

MEASUREMENT OF NASAL PATENCY. Studies have shown a clear effect of intranasal corticosteroids on nasal airway patency.[191] However, an objective measurement of nasal obstruction is rarely used in clinical trials, although it can simply and reliably be recorded by nasal peak flow measurement.

NASAL CYTOLOGY. A nasal smear or a scrape biopsy is a simple way to record inflammation and anti-inflammatory activity of treatment, shown by a reduced number of

mast cells and eosinophils. Such an effect has been proven in several corticosteroid studies,[192,193] but it is rarely used in clinical trials.

CT SCAN OF PARANASAL SINUSES. Lack of effect on sinus pathology is probably a limiting factor for the usefulness of intranasal medication, but apparently this has not been studied in controlled trials.

NASAL RESPONSIVENESS. A few studies have shown that intranasal corticosteroid treatment can reduce nasal hyperresponsiveness in SAR and in perennial rhinitis.[194-196] However, this issue is far less widely studied in rhinitis than in asthma.

EYE SYMPTOMS/ITCHING. Two meta-analyses of intranasal corticosteroids have shown them to be equally effective on eye symptoms as oral antihistamines.[4,178] This surprising observation may be explained by imprecise symptom recording, although it should be noted that the majority of these studies are with intranasal beclomethasone, which has a significant systemic bioavailability (see section on adverse effects of intranasal steroids and effects of intranasal beclomethasone on growth in children). As such, it is probable that the effect on eye symptoms is a reflection of a systemic effect after intranasal therapy.

ASTHMA SYMPTOMS AND LUNG FUNCTION. A mild effect of intranasal corticosteroid on asthma symptoms and on lung function has been shown in some studies.[197,198] This is of considerable theoretical and of some practical interest.

COMPLIANCE: THE PROBLEM OF CONTINUOUS TREATMENT. Patients are pleased with the obvious effect on their nasal complaints, but they will often dislike the idea of continuous treatment. However, a study performed in Helsinki[187] has indicated that intermittent treatment with an intranasal corticosteroid for 2-week periods, given about 5 times a year, can reduce rhinitis symptoms as efficiently as daily treatment with an antihistamine in PAR. This as-needed, periodic treatment may make the use of intranasal corticosteroids more acceptable to the patients and increase patient compliance.

SIDE EFFECTS. Usage for 30 years without a single report of death or of a serious side effect has shown that intranasal corticosteroids are not only highly effective but also very safe. Atrophic rhinitis does not develop, but dryness, crusting, and bleeding in the anterior part of the nose can be a problem. In the rare case, a septal perforation can develop.[170] It is still debated whether long-term use in children can reduce growth.[157,199] This has been suggested by a study of beclomethasone dipropionate used twice daily.[199] However, a twice-daily medication is not necessary to obtain a full antirhinitis effect, and it is more likely to have an effect on growth. This risk can probably be eliminated by using the lowest dose that can control the symptoms by giving the treatment once-daily in the morning and, when disease is controlled, considering the use of intranasal corticosteroids for as-needed, periodic treatment, as described.

Systemic steroids

NASAL SYMPTOMS. It is recommended that the use of systemic corticosteroids for rhinitis be restricted to short periods of 2 to 3 weeks and that these agents be used only in adults. There are very few controlled studies, 4 with depot injections and only 1 with oral treatment.[200] More clinical trials are needed to define the dose-response relationship. Although systemic treatment is highly effective on nasal blockage,[184] limited data have indicated that local treatment is more effective on itching, sneezing, and rhinorrhea.[158] Systemic treatment can be given orally or as a depot injection. Consensus reports recommend oral treatment,[1,4] but there is no reason to assume that the therapeutic index is different.[200] It is a disadvantage of oral treatment that there are no studies to show what is the optimal dosage.

OLFACTION. Undoubtedly, systemic administration is more effective than local administration of corticosteroids on the reduced sense of smell and on sinus pathology in patients with nasal polyposis, but the effect is short-lasting. However, the effect on a reduced sense of smell has been documented only by objective measurements of olfaction in a few studies of nasal polyposis.[121]

OTHER OUTCOME MEASURES. Surprisingly, the effect on nasal cytology and other measures of inflammatory parameters, nasal responsiveness, and sinus pathology has apparently not been studied.[121] Nasal responsiveness has apparently not been studied. A single study has shown an effect on eye symptoms in SAR.[184]

SIDE EFFECTS. Although the side effects of long-term systemic corticosteroid treatment are well known, there is little evidence that treatment of 2 to 3 weeks a few times a year is associated with any significant side effects.[200]

Antihistamines

NASAL SYMPTOMS. The effect of antihistamine treatment is good on sneezing, moderate on rhinorrhea, and poor on blockage.[201] Symptom scoring, attempting to make a precise distinction between these symptoms, is important in clinical trials.

OLFACTION. No studies have shown an effect on this outcome measure, but it is a relevant parameter, considering the claim of an anti-inflammatory effect of second-generation antihistamines.

MEASUREMENT OF NASAL PATENCY. In general, allergen-challenge studies have failed to show any effect of antihistamine pretreatment on nasal blockage when measured objectively.[202-204] On the other hand, Horak et al[205] found some effect after controlled allergen exposure. Objective measures of nasal airway patency have rarely been used in placebo-controlled clinical antihistamine trials, and these published results are negative with regard to nasal airway resistence.[206] However, one recent study with monitoring of nasal airways resistance by active anterior rhinomanometry has shown objective improvement with levocetirizine but not with either desloratadine or placebo.[175]

NASAL CYTOLOGY. Cytology studies are needed to support the claim of an anti-inflammatory action of

antihistamines. There have been several negative studies in this respect,[174,206-208] although 2 recent studies have reported some effects on both inflammatory cell recruitment and cell activation, as reflected by cytokine measures in nasal lavage.[175,176]

NASAL RESPONSIVENESS. One study failed to show any antihistamine effect on allergen-induced nasal hyperresponsiveness.[209] This important parameter has apparently not been studied in other clinical trials.

EYE SYMPTOMS/ITCHING. Several studies have shown efficacy of antihistamines, and eye drops have a quicker onset of action than tablets.[159-161]

SIDE EFFECTS. Serious cardiac arrhythmias have been described for terfenadine and astemizole,[155] but not for other preparations.[210] Although second-generation H_1-antihistamines have considerably reduced central nervous system effects at standard doses in comparison with first-generation agents (see H_1-antihistamine component in clinical outcomes section), cetirizine can be associated with mild sedation.[211] However, drug-comparative studies have also indicated that cetirizine 10 mg/d is a highly effective antihistamine. In one report, astemizole caused a significant increase in weight.[212] Although weighing patients is simple, controlled studies do not seem to exist for other second-generation antihistamines.

Leukotriene receptor antagonists

NASAL SYMPTOMS. Intranasal spraying of cysteinyl leukotrienes can induce nasal blockage, but not itching, sneezing, and rhinorrhea,[213] although leukotrienes are known secretagogues.[214] Consequently, LTRAs can be expected to have only a partial effect on the total symptoms of allergic rhinitis. A study of patients with asthma intolerant to acetylsalicylic acid has shown that inhibition of leukotriene synthesis by a 5-lipoxygenase inhibitor has some effect on nasal blockage and perhaps on the reduced sense of smell in patients who also have nasal polyps.[215] However, the effect of this type of intervention will be more extensive than that achieved with blockade of cysteinyl leukotriene receptors. However, an initial study of treatment with an LTRA in allergic rhinitis with recording of nasal symptoms was disappointing, because no clinical benefit was found with a LTRA as sole therapy.[216] Subsequent, much larger studies have found a statistically significant benefit over placebo, although the magnitude of these effects was not large.[217-220] These studies reported treatment group numbers of between 300 and 1000 patients receiving montelukast or placebo; the substantial study sizes are a reflection of the relative lack of effect of LTRA therapy in the treatment of allergic rhinitis and the large numbers required to discern a small effect over placebo. This contrasts with positive clinical studies in allergic rhinitis with the intranasal corticosteroid budesonide, in which a study group as small as 16 has been able to discern differences from placebo.[221] Consistent with the greater efficacy of intranasal steroids, head-to-head comparisons show significantly greater symptom relief with intranasal steroid therapy in comparison with LTRA therapy.[222] What has been surprising, however, is that these large studies of LTRA therapy have reported improvement not only in nasal obstruction but also in itch, sneeze, and rhinorrhea. Because leukotriene insufflation within the nose does not induce itch or sneeze, these results suggest either that there is a bystander benefit of these symptoms, with improvement reported because other symptoms improve, or that leukotrienes within the nose are having an effect not appreciated by single-dose intranasal challenge studies that influence symptom expression in an indirect manner. This could arise if leukotrienes alter sensory neural stimulation thresholds or modify mast cell activation, both potential explanations for these clinical findings.

OTHER OUTCOME MEASURES. It is not known whether LTRAs have an effect on eosinophil or mast cell accumulation in the nose compared with placebo. An effect on eosinophil recruitment has been shown in the lower airways of patients with asthma.[214] One open study with the LTRA pranlukast has reported a reduction in a range of inflammatory markers in nasal lavage with therapy, but such a study is difficult to interpret and requires appropriate examination.[223] A study of these objective outcome measures is important to find out whether LTRAs possess an anti-inflammatory activity in the nasal mucosa. Histamine does not induce nasal hyperresponsiveness,[224] and it is possible that leukotrienes are important in this respect.[216] Therefore, measurement of nasal responsiveness is relevant in clinical studies of LTRA.

Vasoconstrictors

Isolated vasoconstrictors are not suitable for the treatment of allergic rhinitis, but an oral vasoconstrictor is often used in combination with an antihistamine.

NASAL SYMPTOMS. Vasoconstrictors have a monosymptomatic effect on nasal blockage. The effect of topical treatment is marked, whereas systemic medication has a considerably lower efficacy.[164] A vasoconstrictor spray is very useful in the common cold.

NASAL PATENCY. The need for objective measures of the nasal airway patency is obvious, but nasal patency often is not measured in clinical trials.[164]

SIDE EFFECTS. The risk of development of rhinitis medicamentosa from topical vasoconstrictors is well known, and it limits the treatment to just a few weeks. Systemic vasoconstrictors have a poor therapeutic index, and there are several contraindications to this treatment.[164] It is not elegant pharmacotherapy to constrict every blood vessel in the body to open a blocked nose.

Olfaction and CT scan of paranasal sinuses have not been studied.

Anticholinergic drugs

NASAL SYMPTOMS. Ipratropium bromide has a marked monosymptomatic effect on watery rhinorrhea.[165] Symptom scoring and counting of paper handkerchiefs are the only outcome measures of relevance. Isolated anticholinergics are not suitable for the treatment of allergic

TABLE II. Symptom profiles of major drug types used for allergic rhinitis

	Local antihistimine	Oral antihistimine	Nasal steroid	Systemic steroid
Sneezing	++	++	+++	++
Rhinorrhea	++	++	+++	++
Blockage	+	+	+++	+++
Hyposmia	–	–	+	+++
Eye symptoms	+++	++	+	++
Onset of action	Minutes	1 h	3-12 h	12 h

rhinitis, but they are useful in patients with isolated watery rhinorrhea and in the common cold.

SIDE EFFECTS. A feeling of nasal dryness can occur when the dose of ipratropium bromide is high compared with the secretory activity.[165] This happens regularly because rhinorrhea tends to be intermittent and not continuous.

Combinations of medications

In some severe cases of allergic rhinitis, and in other types of rhinitis, the effect of a single drug, used at the recommended dose, may not be sufficient, and combined drug treatment may be considered. In addition, different drugs have different symptom profiles (Table II). There are surprisingly few controlled clinical studies of combined drug treatment.

Oral antihistamines and vasoconstrictors. Several studies have shown that oral antihistamines are effective on sneezing and rhinorrhea but less effective or not effective on blockage, whereas oral vasoconstrictors have the opposite effect profile.[179-181] Therefore, added treatment has an improved effect on total nasal symptoms,[179-181] and it is often used, although the therapeutic index can be questioned.

Oral antihistamine and LTRA. A combined tablet is a consideration for the simultaneous treatment of rhinitis and asthma. In rhinitis, the antihistamine improves itching, sneezing, and rhinorrhea, and the LTRA may counteract nasal blockage, and perhaps hyperresponsiveness.[214] In asthma, the LTRA inhibits the leukotriene-induced bronchoconstriction, and the antihistamine may have a small additive effect. A placebo-controlled study in SAR has shown an additive effect of the antihistamine, loratadine, and the LTRA montelukast on nasal and, unexpectedly, eye symptoms.[216] However, studies with LTRA/antihistamine combinations have not shown efficacy comparable with intranasal steroid therapy,[225,226] and in one study, these combinations could not be differentiated from antihistamine therapy alone.[35]

Intranasal antihistamine, anticholinergic, and vasoconstrictor. Surprisingly, there are no reports on this combined treatment. It should be useful both in the common cold and in mild cases of allergic rhinitis with occasional symptoms. The vasoconstrictor component will preclude prolonged treatment.

Intranasal corticosteroid and oral antihistamine. It is well documented that intranasal corticosteroids have a better effect on all nasal symptoms than antihistamines.[177,178] However, some highly allergic patients do not obtain adequate nasal symptom control from an intranasal corticosteroid alone at the peak of the pollen season. In these cases, international consensus reports now recommend the combined use of an intranasal corticosteroid and an oral antihistamine.[144] This recommendation seems logical, because the antihistamine counteracts the early-phase histamine-mediated allergic reaction, and the corticosteroid inhibits the late-phase inflammatory reaction. However, this recommendation is not supported by controlled clinical trials. Four double-blind, double-dummy trials in 1250 patients with allergic rhinitis have failed to show any significant difference on nasal symptoms between intranasal corticosteroid with and without oral antihistamine.[227-230] A further recent study has confirmed these findings in SAR.[226] Thus, if this recommendation is followed, it will increase the cost of the treatment without any proven added efficacy on nasal symptoms. Studies need to be performed in those individuals who, despite intranasal steroid therapy administered for sufficiently long to have achieved its maximum benefit, still have residual nasal symptoms to address whether the addition of antihistamines in these patients confers any additional benefit. It is this group that the guidelines refer to, and no data exist to support or refute the use of combination therapy under such circumstances.

Nasal and systemic corticosteroid. For safety reasons, intranasal corticosteroids are preferred to systemic corticosteroids as first-line therapy for allergic rhinitis. When intranasal corticosteroids cannot control the symptoms at the peak of the pollen season in highly allergic patients, systemic corticosteroids are often added. However, there are no controlled clinical data to support this practice. A doubling of the dose of intranasal corticosteroid may be just as effective.

SUMMARY

Clinical trial design is critical if valid information is to be obtained from studies on treatment intervention. Rhinitis carries some confounding variables in addition to those classically considered in therapeutic studies because of the variability in the environmental triggers leading to disease expression. Thus, although randomization and placebo control are standard for assessments of novel intervention, the majority of clinical studies are of a parallel group design rather than crossover design. There is no single objective measurement to define the disease; thus, recruitment for studies is based on the subjective reporting of symptoms by patients. These symptoms are not specific for allergic rhinitis but are also expressed in nonallergic rhinitis, which has a different pathophysiologic basis. On account of this, the variation in allergen exposure between individuals, the intersubject variation in allergenic sensitisation, and the individual subjective

evaluation of symptom severity are considerable sources of variation other than the treatment or placebo in clinical trials. Thus, in general, there is a requirement for large patient populations in studies of naturally occurring disease. Although there is no substitute for these for drug-regulatory purposes, exploration has been made of laboratory allergen challenge models or challenge chamber exposures to help in early drug development *in vivo*, to define therapeutic dose, onset of action, and duration of action, before more definitive clinical studies. These models are based on early or late nasal responses to single intranasal challenge or to repeated nasal allergen challenge in an attempt to mimic the priming and inflammatory mucosal changes that would be acquired in association with repeated daily allergen exposure in naturally occurring disease. Such daily repeated allergen provocations seem to be a sensitive method to assess dose-response effects of both current available topical corticosteroids and new compounds. The outcome from these studies can be clinical, physiologic, or cellular.

Studies of new therapies are initially undertaken in adults, but it is appreciated that rhinitis is particularly common in children and that appropriate treatment is mandatory in this population. One in 5 children worldwide has allergic rhinitis, a disease that significantly affects health, school performance, and quality of life in children. Failure to manage allergic rhinitis effectively in children can lead to complications such as worsening of asthma, sinusitis, and otitis media. Accurate diagnosis of allergic rhinitis in children depends on a thorough history. This includes an assessment of the onset, nature, and duration of symptoms, as well as the presence of specific precipitating factors. Compliance with prescribed therapy is critical to manage allergic rhinitis effectively, with special considerations regarding therapies and educational needs of children and their caregivers. Specific issues arise in children in relation to adverse event monitoring as a result of the additional potential for effects on growth and development.

Subjects with more extensive sinus disease associated with nasal polyposis comprises another specific disease group. This may be part of a more systemic process and may require surgical intervention on account of the extent of the effect of the disease on the normal nasal function and sinus drainage. However, the initial treatment is medical, with intranasal steroids, and a range of outcome measures have shown significant benefit. In addition to the evaluations used for rhinitis is the use of imaging, such as sinus CT scans, and the need for the more invasive direct evaluation by endoscopy.

Finally, there are clinical trial decisions when investigating pharmacologic therapy in naturally occurring allergic rhinitis. Should the therapy be administered prophylactically, or is it most appropriate for symptom relief? Is therapy better administered intranasally or systemically? How does such a decision influence the adverse potential as well as the beneficial clinical response? Should a therapy be given as a sole treatment, or are better results derived from combination therapy? Does the treatment affect the underlying inflammatory process or purely the end-organ symptom response? These and other considerations have been explored in relation to currently available therapies for allergic rhinitis and illustrate the relevance of these considerations to the exploration of novel therapies in this disease area.

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REFERENCES

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108(suppl 5):S147-334.
2. D'Amato G, Ruffilli A, Sacerdoti G, Bonini S. Parietaria pollinosis: a review. Allergy 1992;47:443-9.
3. International consensus report on the diagnosis and management of rhinitis. International Rhinitis Management Working Group. Allergy 1994;49(suppl 19):1-34.
4. van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy 2000;55:116-34.
5. Settipane RA, Lieberman P. Update on nonallergic rhinitis. Ann Allergy Asthma Immunol 2001;86:494-507.
6. Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. J Allergy Clin Immunol 1999;104:927-33.
7. Berkowitz RB, Bernstein DI, LaForce C, Pedinoff AJ, Rooklin AR, Damaraju CR, et al. Onset of action of mometasone furoate nasal spray (NASONEX) in seasonal allergic rhinitis. Allergy 1999;54:64-9.
8. Enberg RN, Ownby DR. Peak nasal inspiratory flow and Wright peak flow: a comparison of their reproducibility. Ann Allergy 1991;67:371-4.
9. Bende M, Carrillo T, Vona I, da Castel-Branco MG, Arheden L. A randomized comparison of the effects of budesonide and mometasone furoate aqueous nasal sprays on nasal peak flow rate and symptoms in perennial allergic rhinitis. Ann Allergy Asthma Immunol 2002;88:617-23.
10. Stern MA, Dahl R, Nielsen LP, Pedersen B, Schrewelius C. A comparison of aqueous suspensions of budesonide nasal spray (128 micrograms and 256 micrograms once daily) and fluticasone propionate nasal spray (200 micrograms once daily) in the treatment of adult patients with seasonal allergic rhinitis. Am J Rhinol 1997;11:323-30.
11. Creticos P, Fireman P, Settipane G, Bernstein D, Casale T, Schwartz H. Intranasal budesonide aqueous pump spray (Rhinocort Aqua) for the treatment of seasonal allergic rhinitis. Rhinocort Aqua Study Group. Allergy Asthma Proc 1998;19:285-94.
12. Meltzer EO. Clinical and antiinflammatory effects of intranasal budesonide aqueous pump spray in the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 1998;81:128-34.
13. Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. J Allergy Clin Immunol 1998;102:902-8.
14. Andersson M, Svensson C, Persson C, Akerlund A, Greiff L. Dose-dependent effects of budesonide aqueous nasal spray on symptoms in a daily nasal allergen challenge model. Ann Allergy Asthma Immunol 2000;85:279-83.
15. Ahlstrom-Emanuelsson C, Persson CG, Svensson C, Andersson M, Hosszu Z, Akerlund A, et al. Establishing a model of seasonal allergic rhinitis and demonstrating dose-response to a topical glucocorticosteroid. Ann Allergy Asthma Immunol 2002;89:159-65.
16. Ahlstrom-Emanuelsson C, Andersson M, Persson C, Schrewelius C, Greiff L. Topical treatment with aqueous solutions of rofleponide palmitate and budesonide in a pollen-season model of allergic rhinitis. Clin Exp Allergy 2004;34:731-5.
17. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. Allergy 1996;51:569-76.

18. Del Carpio J, Kabbash L, Turenne Y, Prevost M, Hebert J, Bedard PM, et al. Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1989;84:741-6.
19. Karlsson G, Runderantz H. Peroral chromones: a new way to treat allergic rhinitis? Acta Otolaryngol Suppl 1979;360:27-9.
20. Kirkegaard J, Secher C, Borum P, Mygind N. Inhibition of histamine-induced nasal symptoms by the H1 antihistamine chlorpheniramine maleate: demonstration of topical effect. Br J Dis Chest 1983;77:113-22.
21. Schumacher MJ, Cota KA, Taussig LM. Pulmonary response to nasal-challenge testing of atopic subjects with stable asthma. J Allergy Clin Immunol 1986;78(1 Pt 1):30-5.
22. Erjefalt I, Persson CG. On the use of absorbing discs to sample mucosal surface liquids. Clin Exp Allergy 1990;20:193-7.
23. Naclerio RM, Meier HL, Kagey-Sobotka A, Adkinson NF Jr, Meyers DA, Norman PS, et al. Mediator release after nasal airway challenge with allergen. Am Rev Respir Dis 1983;128:597-602.
24. Connell JT. Quantitative intranasal pollen challenge, II: effect of daily pollen challenge, environmental pollen exposure, and placebo challenge on the nasal membrane. J Allergy 1968;41:123-39.
25. Greiff L, Pipkorn U, Alkner U, Persson CG. The "nasal pool" device applies controlled concentrations of solutes on human nasal airway mucosa and samples its surface exudations/secretions. Clin Exp Allergy 1990;20:253-9.
26. Greiff L, Meyer P, Svensson C, Persson CG, Andersson M. The "nasal pool"-device for challenge and lavage of the nasal mucosa in children: histamine-induced plasma exudation responses. Pediatr Allergy Immunol 1997;8:137-42.
27. Aas K, Backman A, Belin L, Weeke B. Standardization of allergen extracts with appropriate methods: the combined use of skin prick testing and radio-allergosorbent tests. Allergy 1978;33:130-7.
28. Wang D, Smitz J, Waterschoot S, Clement P. An approach to the understanding of the nasal early-phase reaction induced by nasal allergen challenge. Allergy 1997;52:162-7.
29. Andersson M, Greiff L, Svensson C, Persson C. Various methods for testing nasal responses in vivo: a critical review. Acta Otolaryngol 1995;115:705-13.
30. Andersson M, Nolte H, Baumgarten C, Pipkorn U. Suppressive effect of loratadine on allergen-induced histamine release in the nose. Allergy 1991;46:540-6.
31. Numata T, Konno A, Yamakoshi T, Hanazawa T, Terada N, Nagata H. Comparative role of peptide leukotrienes and histamine in the development of nasal mucosal swelling in nasal allergy. Ann Otol Rhinol Laryngol 1999;108:467-73.
32. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. N Engl J Med 1987;316:1506-10.
33. Andersson M, Andersson P, Pipkorn U. Allergen-induced specific and non-specific nasal reactions: reciprocal relationship and inhibition by topical glucocorticosteroids. Acta Otolaryngol 1989;107:270-7.
34. Wilson AM, Sims EJ, Orr LC, Robb F, Lipworth BJ. An evaluation of short-term corticosteroid response in perennial allergic rhinitis using histamine and adenosine monophosphate nasal challenge. Br J Clin Pharmacol 2003;55:354-9.
35. Lee DK, Jackson CM, Soutar PC, Fardon TC, Lipworth BJ. Effects of single or combined histamine H1-receptor and leukotriene CysLT1-receptor antagonism on nasal adenosine monophosphate challenge in persistent allergic rhinitis. Br J Clin Pharmacol 2004;57:714-9.
36. Klementsson H, Lindqvist N, Andersson M, Pipkorn U. Effect of a single dose of a topical glucocorticoid and a cyclo-oxygenase inhibitor on allergen-induced changes in nasal reactivity. Allergy 1990;45:604-11.
37. Naclerio RM, Bartenfelder D, Proud D, Togias AG, Meyers DA, Kagey-Sobotka A, et al. Theophylline reduces histamine release during pollen-induced rhinitis. J Allergy Clin Immunol 1986;78:874-6.
38. Booij-Noord H, de Vries K, Sluiter HJ, Orie NG. Late bronchial obstructive reaction to experimental inhalation of house dust extract. Clin Allergy 1972;2:43-61.
39. Dahl R. Early and late-phase reactions in the bronchi and nose. In: Mygind N, Pipkorn U, Dahl R, editors. Rhinitis and asthma. Copenhagen: Munksgaard; 1990. p. 203-12.
40. Andersson M, Rimmer J, Salome C, Greiff L, Persson C. Dual symptomatic and exudative nasal responses are not characteristics of perennial allergic rhinitis. Acta Otolaryngol 2001;121:407-13.
41. Pelikan Z. Late and delayed responses of the nasal mucosa to allergen challenge. Ann Allergy 1978;41:37-47.
42. Pipkorn U, Proud D, Lichtenstein LM, Schleimer RP, Peters SP, Adkinson NF Jr, et al. Effect of short-term systemic glucocorticoid treatment on human nasal mediator release after antigen challenge. J Clin Invest 1987;80:957-61.
43. Gronborg H, Bisgaard H, Romeling F, Mygind N. Early and late nasal symptom response to allergen challenge: the effect of pretreatment with a glucocorticosteroid spray. Allergy 1993;48:87-93.
44. Paggiaro PL, Dente FL, Morelli MC, Bancalari L, Di Franco A, Giannini D, et al. Postallergen inhaled budesonide reduces late asthmatic response and inhibits the associated increase of airway responsiveness to methacholine in asthmatics. Am J Respir Crit Care Med 1994;149:1447-51.
45. Miadonna A, Milazzo N, Gibelli S, Salmaso C, Lorini M, Tedeschi A. Nasal response to a single antigen challenge in patients with allergic rhinitis—inflammatory cell recruitment persists up to 48 hours. Clin Exp Allergy 1999;29:941-9.
46. Linden M, Svensson C, Andersson E, Andersson M, Greiff L, Persson CG. Immediate effect of topical budesonide on allergen challenge-induced nasal mucosal fluid levels of granulocyte-macrophage colony-stimulating factor and interleukin-5. Am J Respir Crit Care Med 2000;162:1705-8.
47. Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. J Allergy Clin Immunol 1988;81:580-9.
48. Connell JT. Quantitative intranasal pollen challenges, 3: the priming effect in allergic rhinitis. J Allergy 1969;43:33-44.
49. Andersson M, von Kogerer B, Andersson P, Pipkorn U. Allergen-induced nasal hyperreactivity appears unrelated to the size of the nasal and dermal immediate allergic reaction. Allergy 1987;42:631-7.
50. Davies HJ. Exposure of hay fever subjects to an indoor environmental grass pollen challenge system. Clin Allergy 1985;15:419-27.
51. Horak K, Jager S. The Vienna challenge chamber (VCC)—a new method for allergen exposition tests. Wien Klin Wochenschr 1987;99:509-10.
52. Day JH, Briscoe MP, Clark RH, Ellis AK, Gervais P. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. Ann Allergy Asthma Immunol 1997;79:163-72.
53. Ronborg SM, Mosbech H, Johnsen CR, Poulsen LK. Exposure chamber for allergen challenge: the development and validation of a new concept. Allergy 1996;51:82-8.
54. Wood RA, Eggleston PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. Am J Respir Crit Care Med 1995;151:315-20.
55. Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. J Allergy Clin Immunol 1998;101:638-45.
56. Day JH, Buckeridge DL, Clark RH, Briscoe MP, Phillips R. A randomized, double-blind, placebo-controlled, controlled antigen delivery study of the onset of action of aerosolized triamcinolone acetonide nasal spray in subjects with ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1996;97:1050-7.
57. Day JH, Briscoe MP, Rafeiro E, Ellis AK, Pettersson E, Akerlund A. Onset of action of intranasal budesonide (Rhinocort Aqua) in seasonal allergic rhinitis studied in a controlled exposure model. J Allergy Clin Immunol 2000;105:489-94.
58. Connell JT. A novel method to assess antihistamine and decongestant efficacy. Ann Allergy 1979;42:278-85.
59. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. J Allergy Clin Immunol 1996;97:617-26.
60. Georgitis JW, Meltzer EO, Kaliner M, Weiler J, Berkowitz R. Onset-of-action for antihistamine and decongestant combinations during an outdoor challenge. Ann Allergy Asthma Immunol 2000;84:451-9.

61. Nielsen L, Johnsen CR, Bindslev-Jensen C, Poulsen LK. Efficacy of acrivastine in the treatment of allergic rhinitis during natural pollen exposure: onset of action. Allergy 1994;49:630-6.
62. Donnelly AL, Glass M, Minkwitz MC, Casale TB. The leukotriene D4-receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. Am J Respir Crit Care Med 1995;151:1734-9.
63. Pipkorn U, Karlsson G, Enerback L. Nasal mucosal response to repeated challenges with pollen allergen. Am Rev Respir Dis 1989; 140:729-36.
64. Blackey CH. Experimental researches on the causes and nature of catarrhus aestivus (hay fever or hay asthma). London: Bailliere, Tindall and Cox; 1873.
65. Godthelp T, Fokkens WJ, Kleinjan A, Holm AF, Mulder PG, Prens EP, et al. Antigen presenting cells in the nasal mucosa of patients with allergic rhinitis during allergen provocation. Clin Exp Allergy 1996;26: 677-88.
66. Godthelp T, Holm AF, Fokkens WJ, Doornenbal P, Mulder PG, Hoefsmit EC, et al. Dynamics of nasal eosinophils in response to a nonnatural allergen challenge in patients with allergic rhinitis and control subjects: a biopsy and brush study. J Allergy Clin Immunol 1996;97:800-11.
67. Erjefalt JS, Greiff L, Andersson M, Matsson E, Petersen H, Linden M, et al. Allergen-induced eosinophil cytolysis is a primary mechanism for granule protein release in human upper airways. Am J Respir Crit Care Med 1999;160:304-12.
68. Dykewicz MS, Fineman S. Executive summary of joint task force practice parameters on diagnosis and management of rhinitis. Ann Allergy Asthma Immunol 1998;81:463-8.
69. Katz-Chobert B. Allergic rhinitis in children is often overlooked and undertreated: expert panel recommends improved detection and treatment to reduce effects on children's health and well-being, 1998. Available at: http://www.kidsource.com/kidsource/content5/allergic.rhinitis.html. Accessed November 12, 2004
70. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol 1998;81:478-518.
71. Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. J Allergy Clin Immunol 1997;99:S808-14.
72. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 1994;94:895-901.
73. Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. Thorax 2004;59:855-61.
74. Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. Ann Allergy Asthma Immunol 1999;82: 296-305.
75. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 1994;93: 413-23.
76. Juniper EF. Measuring health-related quality of life in rhinitis. J Allergy Clin Immunol 1997;99:S742-9.
77. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol 1998;101:163-70.
78. Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993;71:121-6.
79. Vuurman EF, van Veggel LM, Sanders RL, Muntjewerff ND, O'Hanlon JF. Effects of semprex-D and diphenhydramine on learning in young adults with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996;76:247-52.
80. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. Ann Allergy Asthma Immunol 2000;84: 403-10.
81. Nimmagadda SR, Evans R 3rd. Allergy: etiology and epidemiology. Pediatr Rev 1999;20:111-5.
82. Newacheck PW, Stoddard JJ. Prevalence and impact of multiple childhood chronic illnesses. J Pediatr 1994;124:40-8.
83. Verdiani P, Di Carlo S, Baronti A. Different prevalence and degree of nonspecific bronchial hyperreactivity between seasonal and perennial rhinitis. J Allergy Clin Immunol 1990;86:576-82.
84. Braman SS, Barrows AA, DeCotiis BA, Settipane GA, Corrao WM. Airway hyperresponsiveness in allergic rhinitis: a risk factor for asthma. Chest 1987;91:671-4.
85. Townley RG, Ryo UY, Kolotkin BM, Kang B. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. J Allergy Clin Immunol 1975;56:429-42.
86. Rachelefsky GS, Siegel SC, Katz RM, Spector SL, Rohr AS. Chronic sinusitis in children. J Allergy Clin Immunol 1991;87:219.
87. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics 1991;87:311-6.
88. Rachelefsky GS, Goldberg M, Katz RM, Boris G, Gyepes MT, Shapiro MJ, et al. Sinus disease in children with respiratory allergy. J Allergy Clin Immunol 1978;61:310-4.
89. Bernstein JM, Lee J, Conboy K, Ellis E, Li P. Further observations on the role of IgE-mediated hypersensitivity in recurrent otitis media with effusion. Otolaryngol Head Neck Surg 1985;93:611-5.
90. Skoner DP. Complications of allergic rhinitis. J Allergy Clin Immunol 2000;105:S605-9.
91. Bresolin D, Shapiro PA, Shapiro GG, Chapko MK, Dassel S. Mouth breathing in allergic children: its relationship to dentofacial development. Am J Orthod 1983;83:334-40.
92. Trask GM, Shapiro GG, Shapiro PA. The effects of perennial allergic rhinitis on dental and skeletal development: a comparison of sibling pairs. Am J Orthod Dentofacial Orthop 1987;92:286-93.
93. Siegel SC. Rhinitis in children. In: Mygind N, Naclerio RM, editors. Allergic and non-allergic rhinitis: clinical aspects. Copenhagen: Munksgaard; 1993. p. 174-83.
94. Meltzer EO, Zeiger RS, Schatz M, Jalowayski AA. Chronic rhinitis in infants and children: etiologic, diagnostic, and therapeutic considerations. Pediatr Clin North Am 1983;30:847-71.
95. Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. J Allergy Clin Immunol 2000;105:S616-21.
96. Smith L. Special considerations for the child with airway disease. J Allergy Clin Immunol 1998;101:S370-2.
97. Menardo JL, Bousquet J, Rodiere M, Astruc J, Michel FB. Skin test reactivity in infancy. J Allergy Clin Immunol 1985;75:646-51.
98. Mygind N. Nasal polyposis. J Allergy Clin Immunol 1990;86:827-9.
99. Keith P, Dolovich J. Allergy and nasal polyposis. In: Mygind N, Lildholt T, editors. Nasal polyposis. Copenhagen: Munksgaard; 1997. p. 68-77.
100. Drake-Lee AB. Medical treatment of nasal polyps. Rhinology 1994;32: 1-4.
101. Lildholt T, Dahl R, Mygind N. Effect of corticosteroids on nasal polyps. In: Mygind N, Lildholt T, editors. Nasal polyposis. Copenhagen: Munksgaard; 1997.
102. Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg 1998;124: 513-8.
103. Amar YG, Frenkiel S, Sobol SE. Outcome analysis of endoscopic sinus surgery for chronic sinusitis in patients having Samter's triad. J Otolaryngol 2000;29:7-12.
104. Jankowski R, Pigret D, Decroocq F. Comparison of functional results after ethmoidectomy and nasalization for diffuse and severe nasal polyposis. Acta Otolaryngol 1997;117:601-8.
105. Naclerio RM, MacKay IS. Guidelines for the management of nasal polyposis. In: Mygind N, Lildholt T, editors. Nasal polyposis. Copenhagen: Munksgaard; 1997. p. 177-80.
106. Holmberg K, Karlsson G. Nasal polyps: surgery of pharmacological intervention? Eur Respir Rev 1994;20:260-5.
107. Lund VJ. Diagnosis and treatment of nasal polyps. BMJ 1995;311: 1411-4.
108. Weschta M, Rimek D, Formanek M, Polzehl D, Podbielski A, Riechelmann H. Topical antifungal treatment of chronic rhinosinusitis with nasal polyps: a randomized, double-blind clinical trial. J Allergy Clin Immunol 2004;113:1122-8.
109. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. Laryngoscope 2004;114:923-30.

110. Dijkstra MD, Ebbens FA, Poublon RM, Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. Clin Exp Allergy 2004;34:1395-400.
111. Bonfils P, Nores JM, Halimi P, Avan P. Medical treatment of stage I nasal polyposis over a 3-year follow-up period. ORL J Otorhinolaryngol Relat Spec 2004;66:27-34.
112. Jankowski R, Bodino C. Olfaction in patients with nasal polyposis: effects of systemic steroids and radical ethmoidectomy with middle turbinate resection (nasalization). Rhinology 2003;41:220-30.
113. Larsen K. The clinical relationship of nasal polyps to asthma. In: Settipane GA, Lund VJ, Bernstein JM, Tos M, editors. Nasal polyps: Epidemiology, pathogenesis and treatment. Providence (RI): OceanSide; 1997.
114. Settipane GA, Settipane RA. Nasal polyps and aspirin intolerance. In: Settipane GA, Lund VJ, Bernstein JM, Tos M, editors. Nasal polyps: epidemiology, pathogenesis and treatment. Providence (RI): OceanSide; 1997.
115. Watelet JB, Annicq B, van Cauwenberge P, Bachert C. Objective outcome after functional endoscopic sinus surgery: prediction factors. Laryngoscope 2004;114:1092-7.
116. Oliverio PJ, Benson ML, Zinreich SJ. Basic sinus imaging and radiological aspects of nasal polyposis. In: Settipane GA, Lund VJ, Bernstein JM, Tos M, editors. Nasal polyps: epidemiology, pathogenesis and treatment. Providence (RI): OceanSide; 1997.
117. Bachert C, van Zele T, Gevaert P, De Schrijver L, Van Cauwenberge P. Superantigens and nasal polyps. Curr Allergy Asthma Rep 2003;3: 523-31.
118. Bernstein JM, Ballow M, Schlievert PM, Rich G, Allen C, Dryja D. A superantigen hypothesis for the pathogenesis of chronic hyperplastic sinusitis with massive nasal polyposis. Am J Rhinol 2003;17:321-6.
119. Perez-Novo CA, Kowalski ML, Kuna P, Ptasinska A, Holtappels G, van Cauwenberge P, et al. Aspirin sensitivity and IgE antibodies to *Staphylococcus aureus* enterotoxins in nasal polyposis: studies on the relationship. Int Arch Allergy Immunol 2004;133:255-60.
120. Drake-Lee A. Magical numbers and the treatment of nasal polyps. Clin Otolaryngol 1996;21:193-7.
121. Lildholdt T, Fogstrup J, Gammelgaard N, Kortholm B, Ulsoe C. Surgical versus medical treatment of nasal polyps. Acta Otolaryngol 1988;105:140-3.
122. Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. Clin Otolaryngol 1995;20:26-30.
123. Lildholdt T, Rundcrantz H, Bende M, Larsen K. Glucocorticoid treatment for nasal polyps: the use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. Arch Otolaryngol Head Neck Surg 1997;123:595-600.
124. Johansson L, Akerlund A, Holmberg K, Melen I, Stierna P, Bende M. Evaluation of methods for endoscopic staging of nasal polyposis. Acta Otolaryngol 2000;120:72-6.
125. Stammberger H. Examination and endoscopy of the nose and paranasal sinuses. In: Mygind N, Lildholt T, editors. Nasal polyposis. Copenhagen: Munksgaard; 1997. p. 120-36.
126. Rasp G, Kramer MF, Ostertag P, Kastenbauer E. [A new system for the classification of ethmoid polyposis: effect of combined local and systemic steroid therapy] [in German]. Laryngorhinootologie 2000;79: 266-72.
127. Frolund L, Madsen F, Mygind N, Nielsen NH, Svendsen UG, Weeke B. Comparison between different techniques for measuring nasal patency in a group of unselected patients. Acta Otolaryngol 1987;104:175-9.
128. Fairley JW, Durham LH, Ell SR. Correlation of subjective sensation of nasal patency with nasal inspiratory peak flow rate. Clin Otolaryngol 1993;18:19-22.
129. Clarke RW, Jones AS. The limitations of peak nasal flow measurement. Clin Otolaryngol 1994;19:502-4.
130. Marais J, Murray JA, Marshall I, Douglas N, Martin S. Minimal cross-sectional areas, nasal peak flow and patients' satisfaction in septoplasty and inferior turbinectomy. Rhinology 1994;32:145-7.
131. Porter MJ, Williamson IG, Kerridge DH, Maw AR. A comparison of the sensitivity of manometric rhinometry, acoustic rhinometry, rhinomanometry and nasal peak flow to detect the decongestant effect of xylometazoline. Clin Otolaryngol 1996;21:218-21.
132. Ahman M. Nasal peak flow rate records in work related nasal blockage. Acta Otolaryngol 1992;112:839-44.
133. Larsen K, Kristensen S. Peak flow nasal patency indices and self-assessment in septoplasty. Clin Otolaryngol 1990;15:327-34.
134. Wihl JA, Malm L. Rhinomanometry and nasal peak expiratory and inspiratory flow rate. Ann Allergy 1988;61:50-5.
135. Holmstrom M, Scadding GK, Lund VJ, Darby YC. Assessment of nasal obstruction: a comparison between rhinomanometry and nasal inspiratory peak flow. Rhinology 1990;28:191-6.
136. Cote J, Cartier A, Malo JL, Rouleau M, Boulet LP. Compliance with peak expiratory flow monitoring in home management of asthma. Chest 1998;113:968-72.
137. Deems DA, Doty RL, Settle RG, Moore-Gillon V, Shaman P, Mester AF, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. Arch Otolaryngol Head Neck Surg 1991;117:519-28.
138. Doty RL. Olfaction. In: Mygind N, Lildholdt T, editors. Nasal polyposis. Copenhagen: Munksgaard; 1997. p. 153-9.
139. Klimek L, Moll B, Amedee RG, Mann WJ. Olfactory function after microscopic endonasal surgery in patients with nasal polyps. Am J Rhinol 1997;11:251-5.
140. Moore-Gillon V. Olfactory and the sense of smell. In: Mackay I, editor. Rhinitis: mechanisms and management. London: Royal Society of Medicine Services Ltd; 1989. p. 69-79.
141. Auffermann H, Gerull G, Mathe F, Mrowinski D. Olfactory evoked potentials and contingent negative variation simultaneously recorded for diagnosis of smell disorders. Ann Otol Rhinol Laryngol 1993;102: 6-10.
142. Simpson WA. The method of constant stimuli is efficient. Percept Psychophys 1988;44:433-6.
143. Akerlund A, Bende M, Murphy C. Olfactory threshold and nasal mucosal changes in experimentally induced common cold. Acta Otolaryngol 1995;115:88-92.
144. Delank KW, Stoll W. Olfactory function after functional endoscopic sinus surgery for chronic sinusitis. Rhinology 1998;36:15-9.
145. Kenriksdottir I, Murphy C, Bende M. Olfactory threshold after nasal allergen challenge. ORL J Otorhinolaryngol Relat Spec 1997; 59:36-8.
146. Radenne F, Lamblin C, Vandezande LM, Tillie-Leblond I, Darras J, Tonnel AB, et al. Quality of life in nasal polyposis. J Allergy Clin Immunol 1999;104:79-84.
147. Derekoylu L, Canakcioglu S, Mamak A, Guvenc MG, Banitahmaseb A. [Quality of life assessment with the use of the SF-36 in patients with nasal polyposis: correlations with clinical and laboratory findings] [in Turkish]. Kulak Burun Bogaz Ihtis Derg 2003;11:72-9.
148. Greiff L, Erjefalt JS, Andersson M, Svensson C, Persson C. Microvascular exudation of plasma and epithelial shedding-restitution processes as causative events in inflammatory airways diseases. In: Mygind N, Lildholt T, editors. Nasal polyposis. Copenhagen: Munksgaard; 1997. p. 50-60.
149. Kanai N, Denburg J, Jordana M, Dolovich J. Nasal polyp inflammation: effect of topical nasal steroid. Am J Respir Crit Care Med 1994;150: 1094-100.
150. Mackay I, Lund VJ. Imaging and staging. In: Mygind N, Lildholdt T, editors. Nasal polyposis. Copenhagen: Munksgaard; 1997.
151. Rowe-Jones J, Mackay I, Colquhoun I. Charing Cross CT protocol for endoscopic sinus surgery. J Laryngol Otol 1995;109:1057-60.
152. van Camp C, Clement PA. Results of oral steroid treatment in nasal polyposis. Rhinology 1994;32:5-9.
153. O'Flynn P. Acoustic rhinometry: validation of volume changes following intra-nasal polypectomy. Clin Otolaryngol 1993;18:423-5.
154. Elbrond O, Felding JU, Gustavsen KM. Acoustic rhinometry used as a method to monitor the effect of intramuscular injection of steroid in the treatment of nasal polyps. J Laryngol Otol 1991;105:178-80.
155. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine-ketoconazole interaction: pharmacokinetic and electrocardiographic consequences. JAMA 1993;269:1513-8.
156. Mygind N, Lund V. Topical corticosteroid therapy of rhinitis: a review. Clin Immunother 1996;5:122-36.
157. Passalacqua G, Albano M, Canonica GW, Bachert C, Van Cauwenberge P, Davies RJ, et al. Inhaled and nasal corticosteroids: safety aspects. Allergy 2000;55:16-33.

158. Pichler WJ, Klint T, Blaser M, Graf W, Sauter K, Weiss S, et al. Clinical comparison of systemic methylprednisolone acetate versus topical budesonide in patients with seasonal allergic rhinitis. Allergy 1988;43:87-92.
159. Sohoel P, Freng BA, Kramer J, Poppe S, Rebo R, Korsrud FR, et al. Topical levocabastine compared with orally administered terfenadine for the prophylaxis and treatment of seasonal rhinoconjunctivitis. J Allergy Clin Immunol 1993;92:73-81.
160. A comparison of topical levocabastine and oral terfenadine in the treatment of allergic rhinoconjunctivitis. The Livostin Study Group. Allergy 1993;48:530-4.
161. Topical levocabastine compared with oral loratadine for the treatment of seasonal allergic rhinoconjunctivitis. Swedish GP Allergy Team. Allergy 1994;49:611-5.
162. Trigg CJ, Davies RJ. Local antihistamines. Clin Exp Allergy 1996;26: 1108-11.
163. Stokes TC, Feinberg G. Rapid onset of action of levocabastine eye-drops in histamine-induced conjunctivitis. Clin Exp Allergy 1993;23:791-4.
164. Eccles R. Nasal airflow and decongestants. In: Naclerio RM, Durham SR, Mygind N, editors. Rhinitis: mechanisms and management. New York: Marcel Dekker; 1999. p. 291-312.
165. Mygind N, Borum P, Baroody FM, Naclerio RM. Anticholinergic medication. In: Naclerio RM, Durham LH, Mygind N, editors. Rhinitis: mechanisms and management. New York: Marcel Dekker; 1999. p. 313-34.
166. Newman SP, Moren F, Clarke SW. Deposition pattern from a nasal pump spray. Rhinology 1987;25:77-82.
167. Toft A, Wihl JA, Toxman J, Mygind N. Double-blind comparison between beclomethasone dipropionate as aerosol and as powder in patients with nasal polyposis. Clin Allergy 1982;12:391-401.
168. Hallen H, Graf P. Benzalkonium chloride in nasal decongestive sprays has a long-lasting adverse effect on the nasal mucosa of healthy volunteers. Clin Exp Allergy 1995;25:401-5.
169. Braat JP, Ainge G, Bowles JA, Richards DH, Van Riessen D, Visser WJ, et al. The lack of effect of benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study. Clin Exp Allergy 1995;25:957-65.
170. Mygind N, Naclerio RM. Intranasal corticosteroids. In: Naclerio RM, Durham LH, Mygind N, editors. Rhinitis: mechanisms and management. New York: Marcel Dekker; 1999. p. 221-56.
171. Lund V, Aaronson D, Bousquet J. International consensus report on the diagnosis and management of rhinitis. Allergy 1994;49(suppl 19): 1-34.
172. Puhakka T, Makela MJ, Malmstrom K, Uhari M, Savolainen J, Terho EO, et al. The common cold: effects of intranasal fluticasone propionate treatment. J Allergy Clin Immunol 1998;101:726-31.
173. Church MK. Non-H1-receptor effects of antihistamines. Clin Exp Allergy 1999;29(suppl 3):39-48.
174. Di Lorenzo G, Gervasi F, Drago A, Esposito Pellitteri M, Di Salvo A, Cosentino D, et al. Comparison of the effects of fluticasone propionate, aqueous nasal spray and levocabastine on inflammatory cells in nasal lavage and clinical activity during the pollen season in seasonal rhinitics. Clin Exp Allergy 1999;29:1367-77.
175. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. Clin Exp Allergy 2004;34: 958-64.
176. Ciprandi G, Tosca MA, Milanese M, Ricca V. Cetirizine reduces cytokines and inflammatory cells in children with perennial allergic rhinitis. Allerg Immunol (Paris) 2004;36:237-40.
177. Stempel DA, Thomas M. Treatment of allergic rhinitis: an evidence-based evaluation of nasal corticosteroids versus nonsedating antihistamines. Am J Manag Care 1998;4:89-96.
178. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998;317:1624-9.
179. Bronsky E, Boggs P, Findlay S, Gawchik S, Georgitis J, Mansmann H, et al. Comparative efficacy and safety of a once-daily loratadine-pseudoephedrine combination versus its components alone and placebo in the management of seasonal allergic rhinitis. J Allergy Clin Immunol 1995;96:139-47.
180. Sussman GL, Mason J, Compton D, Stewart J, Ricard N. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. J Allergy Clin Immunol 1999; 104:100-6.
181. Grosclaude M, Mees K, Pinelli ME, Lucas M, Van de Venne H. Cetirizine and pseudoephedrine retard, given alone or in combination, in patients with seasonal allergic rhinitis. Rhinology 1997;35:67-73.
182. Borum S, Nielsen K, Bisgaard H, Mygind N. Experimentally induced nasal hypersecretion does not reduce the efficacy of intranasal levocabastine. Rhinology 1998;36:153-5.
183. Tarlo SM, Cockcroft DW, Dolovich J, Hargreave FE. Beclomethasone dipropionate aerosol in perennial rhinitis. J Allergy Clin Immunol 1977; 59:232-6.
184. Borum P, Gronborg H, Mygind N. Seasonal allergic rhinitis and depot injection of a corticosteroid: evaluation of the efficacy of medication early and late in the season based on detailed symptom recording. Allergy 1987;42:26-32.
185. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. BMJ 1973;4:464-6.
186. Mygind N, Pedersen CB, Prytz S, Sorensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. Clin Allergy 1975;5:159-64.
187. Rinne J, Simola M, Malmberg H, Haahtela T. Early treatment of perennial rhinitis with budesonide or cetirizine and its effect on long-term outcome. J Allergy Clin Immunol 2002;109:426-32.
188. Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991;325:388-92.
189. Naclerio RM, Adkinson NF Jr, Creticos PS, Baroody FM, Hamilton RG, Norman PS. Intranasal steroids inhibit seasonal increases in ragweed-specific immunoglobulin E antibodies. J Allergy Clin Immunol 1993;92:717-21.
190. Tos M, Svendstrup F, Arndal H, Orntoft S, Jakobsen J, Borum P, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. Am J Rhinol 1998;12: 183-9.
191. Mygind N, Dahl R, Nielsen LP, Hilberg O, Bjerke T. Effect of corticosteroids on nasal blockage in rhinitis measured by objective methods. Allergy 1997;52(suppl 40):39-44.
192. Meltzer EO, Orgel HA, Rogenes PR, Field EA. Nasal cytology in patients with allergic rhinitis: effects of intranasal fluticasone propionate. J Allergy Clin Immunol 1994;94:708-15.
193. Klementsson H, Svensson C, Andersson M, Venge P, Pipkorn U, Persson CG. Eosinophils, secretory responsiveness and glucocorticoid-induced effects on the nasal mucosa during a weak pollen season. Clin Exp Allergy 1991;21:705-10.
194. Malm L, Wihl JA, Lamm CJ, Lindqvist N. Reduction of metacholine-induced nasal secretion by treatment with a new topical steroid in perennial non-allergic rhinitis. Allergy 1981;36:209-14.
195. Studham JM, O'Connell F, Henderson J, Thomas VE, Fuller RW, Pride NB, et al. Effect of topical beclomethasone on histamine-induced increases in nasal airflow resistance and secretion in perennial rhinitis. Clin Otolaryngol 1993;18:285-90.
196. Birchall MA, Henderson JC, Studham JM, Phillips I, Pride NB, Fuller RW. The effect of topical fluticasone propionate on intranasal histamine challenge in subjects with perennial allergic rhinitis. Clin Otolaryngol 1995;20:204-10.
197. Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. Am Rev Respir Dis 1984;130:1014-8.
198. Reed CE, Marcoux JP, Welsh PW. Effects of topical nasal treatment on asthma symptoms. J Allergy Clin Immunol 1988;81:1042-7.
199. Skoner DP, Rachelefsky GS, Meltzer EO, Chervinsky P, Morris RM, Seltzer JM, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics 2000; 105:E23.
200. Mygind N, Laursen LC, Dahl M. Systemic corticosteroid treatment for seasonal allergic rhinitis: a common but poorly documented therapy. Allergy 2000;55:11-5.
201. Simons FE, Simons KJ. Clinical pharmacology of new histamine H1 receptor antagonists. Clin Pharmacokinet 1999;36:329-52.

202. Jankowski R, Wagenmann M, Baroody FM, Naclerio R. Effect of terfenadine on nasal provocation. Int Arch Allergy Immunol 1993;101: 311-7.
203. Hilberg O, Grymer LF, Pedersen OF. Nasal histamine challenge in nonallergic and allergic subjects evaluated by acoustic rhinometry. Allergy 1995;50:166-73.
204. Thomas KE, Ollier S, Ferguson H, Davies RJ. The effect of intranasal azelastine, Rhinolast, on nasal airways obstruction and sneezing following provocation testing with histamine and allergen. Clin Exp Allergy 1992;22:642-7.
205. Horak K, Jager S, Toth J, Berger U, Nimberger E. Azelastine in pollen-induced allergic rhinitis. Drug Invest 1994;7:34-40.
206. Bronsky EA, Dockhorn RJ, Meltzer EO, Shapiro G, Boltansky H, LaForce C, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1996;97:915-21.
207. Jordana G, Dolovich J, Briscoe MP, Day JH, Drouin MA, Gold M, et al. Intranasal fluticasone propionate versus loratadine in the treatment of adolescent patients with seasonal allergic rhinitis. J Allergy Clin Immunol 1996;97:588-95.
208. Pelucchi A, Chiapparino A, Mastropasqua B, Marazzini L, Hernandez A, Foresi A. Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens. J Allergy Clin Immunol 1995;95:515-23.
209. de Graaf-in 't Veld T, Garrelds IM, van Toorenenbergen AW, Mulder PG, Gerth van Wijk R, Boegheim JP. Effect of topical levocabastine on nasal response to allergen challenge and nasal hyperreactivity in perennial rhinitis. Ann Allergy Asthma Immunol 1995;75:261-6.
210. Yap YG, Camm AJ. The current cardiac safety situation with antihistamines. Clin Exp Allergy 1999;29(suppl 1):15-24.
211. Falliers CJ, Brandon ML, Buchman E, Connell JT, Dockhorn R, Leese PT, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. Ann Allergy 1991;66:257-62.
212. Wihl JA, Petersen BN, Petersen LN, Gundersen G, Bresson K, Mygind N. Effect of the nonsedative H1-receptor antagonist astemizole in perennial allergic and nonallergic rhinitis. J Allergy Clin Immunol 1985;75:720-7.
213. Howarth PH. Leukotrienes in rhinitis. Am J Respir Crit Care Med 2000; 161:S133-6.
214. Mygind N, Dahl R, Bisgaard H. Leukotrienes, leukotriene receptor antagonists, and rhinitis. Allergy 2000;55:421-4.
215. Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. Am J Respir Crit Care Med 1998;157:1187-94.
216. Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol 2000;105:917-22.
217. Philip G, Malmstrom K, Hampel FC, Weinstein SF, LaForce CF, Ratner PH, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. Clin Exp Allergy 2002;32:1020-8.
218. van Adelsberg J, Philip G, LaForce CF, Weinstein SF, Menten J, Malice MP, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2003;90:214-22.
219. van Adelsberg J, Philip G, Pedinoff AJ, Meltzer EO, Ratner PH, Menten J, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. Allergy 2003;58:1268-76.
220. Chervinsky P, Philip G, Malice MP, Bardelas J, Nayak A, Marchal JL, et al. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. Ann Allergy Asthma Immunol 2004;92: 367-73.
221. Svensson C, Andersson M, Greiff L, Blychert LO, Persson CG. Effects of topical budesonide and levocabastine on nasal symptoms and plasma exudation responses in seasonal allergic rhinitis. Allergy 1998;53: 367-74.
222. Ratner PH, Howland WC 3rd, Arastu R, Philpot EE, Klein KC, Baidoo CA, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. Ann Allergy Asthma Immunol 2003;90:536-42.
223. Ueda T, Takeno S, Furukido K, Hirakawa K, Yajin K. Leukotriene receptor antagonist pranlukast suppresses eosinophil infiltration and cytokine production in human nasal mucosa of perennial allergic rhinitis. Ann Otol Rhinol Laryngol 2003;112:955-61.
224. Gronborg H, Borum P, Mygind N. Histamine and methacholine do not increase nasal reactivity. Clin Allergy 1986;16:597-602.
225. Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:949-55.
226. Di Lorenzo G, Pacor ML, Pellitteri ME, Morici G, Di Gregoli A, Lo Bianco C, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. Clin Exp Allergy 2004;34:259-67.
227. Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 1989;83:627-33.
228. Benincasa C, Lloyd RS. Evaluation of fluticasone propionate aqueous nasal spray taken alone or in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. Drug Invest 1994; 8:225-33.
229. Simpson RJ. Budesonide and terfenadine, separately and in combination, in the treatment of hay fever. Ann Allergy 1994;73:497-502.
230. Ratner PH, van Bavel JH, Martin BG, Hampel FC Jr, Howland WC 3rd, Rogenes PR, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. J Fam Pract 1998;47: 118-25.