

Clinical outcomes and adverse effect monitoring in allergic rhinitis

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The subjective recording in diary cards of symptoms of itch, sneeze, nose running, and blockage, with the use of a rating scale to indicate the level of severity, is usual for clinical trials in allergic rhinitis. The primary outcome measure is usually a composite score that enables a single total symptoms score endpoint. It is appreciated, however, that rhinitis has a greater effect on the individual than is reflected purely by the recording of anterior nasal symptoms. Nasal obstruction is troublesome and may lead to sleep disturbance in addition to impaired

daytime concentration and daytime sleepiness. These impairments affect school and work performance. Individuals with rhinitis find it socially embarrassing to be seen sneezing, sniffing, or blowing their nose. To capture these and other aspects of the disease-specific health-related quality of life, questionnaires such as the Rhinoconjunctivitis Quality of Life Questionnaire have been developed and validated for clinical trial use. The adoption of health-related quality of life questionnaires into clinical trials broadens the information obtained regarding the effect of the therapeutic intervention and helps focus on issues relevant to the individual patient. It must be appreciated that it is not only the disease that may adversely affect health-related quality of life; administered therapy, although intended to be beneficial, may also cause health impairment. Adverse-event monitoring is thus essential in clinical trials.

The first-generation H₁-histamines, because of their effect on central H₁-receptors, are classically associated with central nervous system (CNS) effects such as sedation. Although this is not always perceived by the patient, it is clearly evident with objective performance testing, and positron emission tomography scanning has directly demonstrated the central H₁-receptor occupancy. The second-generation H₁-antihistamines have reduced central H₁-receptor occupancy and considerably reduced or absent CNS sedative effects. Therefore, the CNS effects are entirely avoidable, and the first-generation H₁-antihistamines should no longer be used in the management of allergic rhinitis. The considerably rarer but potentially very serious cardiac arrhythmogenic effects of H₁-antihistamines are appreciated to be molecule-specific rather than class-specific. The *in vitro* screening of new compounds to eliminate the further development of those with cardiotoxicity ideally will lead to this adverse effect being historic. The incorporation of electrocardiogram recording in clinical trials provides direct information relating to prolongation of QT interval corrected for heart rate.

Although administered at low doses, intranasal steroids still have the potential for systemic absorption and adverse consequences. However, it is appreciated that meaningful differences exist in the bioavailability of different steroid molecules, and although a small but statistically significant effect on growth in children has been identified with the long-term use of intranasal beclomethasone when administered twice daily for 1 year, this is not evident with all intranasal steroids. In addition, twice-daily intranasal steroid administration may have more effect—from the endocrinologic perspective—than once-daily administration in the morning, which coincides better with the natural diurnal variation in cortisol. Thus, once-daily intranasal steroid administration is preferable, and when used in studies in children, measurement of height change during the study period is an important outcome variable together with other indices of systemic steroid

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bioavailability (eg, tests of hypothalamic-pituitary-adrenal axis function). These considerations have even greater relevance if children are concurrently also receiving inhaled steroids for asthma, because the total steroid load will be greater. (*J Allergy Clin Immunol* 2005;115:S390-413.)

Key words: Rhinitis, allergy, symptom recording, clinical trials, health-related quality of life, questionnaire, olfaction, sense of smell testing, H_1 -antihistamines, CNS sedation, cardiotoxicity, intranasal steroids, systemic side effects, HPA axis, children, growth, bone metabolism

NASAL SYMPTOM RECORDING

Clinical trials in allergic rhinitis standardly involve patients recording their nasal symptoms in daily diary cards, with separate recording of the severity of their symptoms of nasal itch, sneeze, nasal discharge, and nasal obstruction. Classically, simple rating scales from 0 to 3 are used, with defined criteria to assign the appropriate rating, such as 0 = no symptoms, 1 = mild symptoms (symptoms that are present but not particularly bothersome), 2 = moderate symptoms (symptoms that are bothersome but do not interfere with daily activities), and 3 = severe symptoms (symptoms that are bothersome and interfere with daily activities or disturb sleep).

Alternative methods of symptom reporting have also been used, such as 10-cm visual analogue scales with defined limits—for example, “no symptoms” and “worst-ever symptoms.” Such an approach allows the use of a continuous variable scale rather than an interrupted scale but is disadvantaged by a tendency in recording to avoid the extremes of the scale, thereby narrowing the spectrum of response. Furthermore, the recordings require accurate measurement and are thus more labor-intensive to analyze. Additional outcomes, such as global evaluation of effectiveness at the end of the trial by the patient and investigator, have been used, but when this latter outcome is based on the subjective reporting by patients of their sense of well-being, the investigator assessment can only mimic that of the patient and is of little value.

A Draft Guidance document provided by the US Department of Health and Human Services Food and Drug Administration, Allergic Rhinitis: Clinical Development Programs for Drug Products (www.fda.gov/cder/guidance/2718dft.htm) recommends the use of rating scale self-assessment by patients as the primary outcome, with an overall summed symptom score of individual symptoms of nasal itch, sneeze, rhinorrhea, and congestion to provide a composite single symptom score. Both an instantaneous symptom score (ie, an evaluation of symptom severity immediately before the next dose of medication) and a reflective symptom score (ie, an evaluation of symptom severity over a predefined period such as 12 hours or 24 hours) are suggested. These measures provide information about whether the administered medication still provides symptom relief at the end of its dosing regimen compared with placebo, and also

Abbreviations used

AML:	Ascending methods of limits procedure
BMD:	Bone mineral density
CNS:	Central nervous system
FDA:	US Food and Drug Administration
HPA:	Hypothalamic-pituitary-adrenal
HRQL:	Health-related quality of life
ICS:	Inhaled corticosteroid
INS:	Intranasal steroid
MRI:	Magnetic resonance imaging
PEA:	Phenyl ethyl alcohol
PET:	Positron emission tomography
QOL:	Quality of life
QTc:	QT interval corrected for heart rate
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S):	Standardised Rhinoconjunctivitis Quality of Life Questionnaire
SAR:	Seasonal allergic rhinitis
SF-36:	Medical Outcomes Survey Short Form 36
SS:	Single staircase procedure
STT:	Smell Threshold Test
UPSIT:	University of Pennsylvania Smell Identification Test

provide information on the overall magnitude of effect of the therapeutic intervention throughout the treatment period.¹ Individual symptom parameters can also be evaluated separately as secondary endpoints. The bases for the recommendation that subjective symptom reporting is the most appropriate endpoint are that such an approach is the best validated method and that alternatives are less substantiated.

This method of evaluation provides insight into the specific nasal symptoms surveyed but does not provide any insight into the overall effect of the disease on the individual and thus provides limited information. For example, although adults with rhinitis and rhinoconjunctivitis are certainly bothered by the symptoms themselves, particularly having a stuffy/blocked nose, a runny nose, and sneezing, they are also bothered by not being able to sleep well at night and the consequences of feeling tired during the day. A recent study compared the daytime sleepiness score, based on the Epworth Sleepiness Scale, and outcomes from formal polysomnography sleep studies in adult subjects with seasonal allergic rhinitis (SAR) and a matched group of healthy control subjects.² The study found that daytime sleepiness was a feature of allergic rhinitis and that this related both to severity of disease and to impairment in quality of life (QOL). Although there were statistically significant effects of SAR on selected sleep parameters, when the effects were monitored objectively, the authors felt that these were minor and not clinically relevant, and concluded that the daytime sleepiness was a feature of the allergic disease per se and not related to disturbed nocturnal sleep. However, such a conclusion is questioned by the results of an open study in children showing that the introduction of intranasal budesonide as a therapy for persistent allergic

rhinitis not only improved nasal symptoms, including nasal obstruction, but also markedly reduced the mean number of sleep arousals per hour (all apneas and hypopneas), suggesting that improving nasal congestion in patients with allergic rhinitis can objectively improve sleep parameters.³ In this study, there was an associated improvement in daytime QOL. It is recognized that patients with allergic rhinitis also have other nonnasal symptoms that are troublesome, such as thirst, poor concentration, and headache. They find practical problems annoying (having to carry tissues, always having to blow their nose, and so forth), they are limited in their daily activities, and they feel frustrated and irritable.⁴ In an attempt to encompass all of these aspects, specific QOL indices have been constructed that encompass both nasal and nonnasal domains.⁴ Such indices explore more profoundly the effect of the disease on the individual and may thus better reflect the effect of the disease and also the effect of therapeutic intervention.

QOL EVALUATION IN RHINITIS

Quality of life is a rather nebulous expression often meaning different things to different people, and this has made defining QOL difficult. However, most clinicians agree that many factors, such as finances, spirituality, and health contribute to QOL while also affecting each other. Taken very simply, health-related QOL (HRQL) is the component of overall QOL that is determined primarily by the person's health and that can be influenced by clinical interventions. For simplicity and focus, the definition by Schipper and Powell⁵ is very fitting: "the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient." The final phrase is important because it emphasizes that these are the impairments that the patients themselves consider important. If one accepts the 3 reasons for treating patients—to prevent mortality, to reduce the probability of future morbidity, and to improve patient well-being⁶—then it is quite apparent that for the majority of patients with rhinitis, improving patient well-being or, in other words, improving their HRQL will be the primary goal of treatment.

Several different outcome measures have been used to assess the clinical status of the nose. These measures include indices such as nasal symptom severity, as discussed, as well as objective measures relating to specific aspects of nasal function and status, including rhinomanometry, nasal cytology, and nasal hyperreactivity.^{7,8} These measures are important in providing detailed information about specific aspects of the nose itself but do not provide an estimate of the impact on patients' daily functioning, and as such, at best there are only weak to moderate correlations between conventional clinical markers of nasal inflammation and the patient's rhinitis-specific QOL.^{4,8} It is thus necessary to have a measure of HRQL to identify the effect of rhinitis on daily functioning and to evaluate whether treatment produces an improvement. This cannot be imputed from the conventional

clinical indices. The use of such HRQL indices has highlighted that rhinitis can be very troublesome to patients and can cause severe impairment of HRQL.⁹ The degree of impairment is often substantially more than many people without rhinitis would have anticipated.

Measurement of HRQL in rhinitis

The recognition of the importance of HRQL, the poor correlation between the conventional clinical indices of nasal impairment and HRQL, and the advent of HRQL instruments with strong measurement properties have already ensured that many rhinitis clinical trials include an assessment of HRQL as one of the primary endpoints.¹⁰⁻¹⁴ These instruments are short, easily understood, and usually in self-administered format, making completion simple for both investigator and patient. Experience has indicated that patients appreciate completing HRQL questionnaires because they can relate to the questions and know that the things important to them are being taken into consideration. A variety of valid instruments for measuring HRQL in patients with rhinitis has been established. There is no best instrument. Each instrument has been developed for a different purpose and will have different measurement properties. In principle, there are 2 types of HRQL questionnaires: generic and specific.

Generic QOL questionnaires

Generic instruments are designed to be applicable to patients with all kinds of medical conditions. The most commonly used and the best validated is the Medical Outcomes Survey Short Form 36 (SF-36).¹⁵ The SF-36 contains 9 domains that can be combined into 2 primary functions, mental and physical, and does not ask disease-specific questions.

This lack of specificity confers an advantage to generic instruments in that burden of illness can be compared across different medical conditions. For instance, it is possible to compare the burden of illness of patients with rhinitis, asthma, and chronic obstructive pulmonary disease by using the same questionnaire instrument. Such questionnaires thus must be broad in their comprehensiveness. The disadvantage of such generic instruments is that they are insensitive because they have very little depth, and thus, impairments important to patients with a specific condition may not be included. Consequently, in many conditions, including rhinitis, a generic instrument is often unresponsive to changes in HRQL that are small but important to patients.^{9,16,17} Therefore the use of generic instruments is limited and not appropriate for clinical trials and clinical practice, in which examination of the effect of treatment within individuals or groups of patients with the same disease is required.

This lack in depth of focus of the generic instruments has led to the development of specific instruments. Such instruments may be specific for a group of patients (eg, the elderly), a particular function (eg, pain, age), or a disease (eg, rhinitis). Disease-specific instruments have been developed by interviewing patients and identifying the impairments that are most important to them. These

instruments thus focus on the problems that are most troublesome and those that represent appropriate targets for interventions. As a result, disease-specific instruments are much more likely to detect small but clinically important changes in patients' problems.

Specific QOL questionnaires

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was designed specifically to evaluate HRQL in adults with rhinoconjunctivitis⁴ by asking patients to identify those items that were most troublesome to them. The final 28-item RQLQ covers the following 7 domains: sleep (3 items), non-nasal/eye symptoms (7 items), practical problems (3 items), nasal symptoms (4 items), eye symptoms (4 items), activities that have been limited by nose or eye symptoms (3 items), and emotional function (4 items). Subjects are asked to rate each of the items on a scale of 0 to 6 (in which 0 = not troubled and 6 = extremely troubled). The mean value for each domain is calculated, as well as overall HRQL including all items. A high score indicates poor QOL. An abbreviated version of this RQLQ, the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ), has been validated more recently and has been reduced to 14 questions spanning 5 separate domains (activity limitations, practical problems, nose symptoms, eye symptoms, and other symptoms).¹⁸

Specific instruments for different age groups of patients with rhinitis have also been developed. The Standardised Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)),⁴ the MiniRQLQ,¹⁸ and a Rhinitis Quality of Life Questionnaire¹⁹ have been tested in adult patients with seasonal and perennial allergic rhinitis. A further adolescent RQLQ questionnaire has been developed, covering patients in the age range of 12 to 17 years, which takes into account that adolescents may have limitations different from those of adults.²⁰ This questionnaire is a slightly modified version of the adult version, because problems in doing schoolwork and generally not feeling well have been found to be more relevant to adolescents than adults. The Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) has been developed for children age 6 to 12 years.²¹ This questionnaire differs from others because children are less bothered by emotional problems. These specific questionnaires have allowed the exploration of the effect of the disease and have also allowed exploration of the extent of benefit with a range of interventions.

Comparison of specific and generic HRQL measures in rhinitis

The RQLQ(S) has been shown to be a more responsive (sensitive to change) instrument in measuring HRQL in patients with rhinitis than generic instruments. In one study, the RQLQ(s) and SF-36 were used to compare 2 steroid treatments and placebo, and the responsiveness of the former was superior to that of the SF-36 (Fig 1).^{13,14} A study by Juniper et al²² compared the RQLQ(S) with 3 other QOL indices—the gamble, the rating, and the SF-

36—in adult patients with rhinoconjunctivitis. Both the RQLQ(S) and rating scale had strong evaluative and discriminatory properties, the SF-36 had poor evaluative properties and only acceptable discriminatory properties, and the gamble scale performed poorly. On both reliability and responsiveness, the RQLQ(S) scored the highest and was thus considered the best of the indices studied.

Reproducibility and discriminatory ability of RQLQ and MiniRQLQ: response to treatment

The usefulness of the RQLQ(S) as an index of response to treatment is suggested by a study in which patients who had self-managed their rhinitis demonstrated significant improvements in 6 of the 7 domains of the RQLQ(S) when their care was taken over by board-certified allergy specialists,²³ indicating an impairment in HRQL when they were self-managing that had not been appreciated. The validity of the RQLQ as an outcome measure has been formally assessed in a large number of treatment intervention studies involving H₁-antihistamines, anti-leukotrienes, and intranasal corticosteroids. Placebo-controlled studies in seasonal allergic rhinitis (SAR) have identified significant improvements in RQLQ with the H₁-antihistamines fexofenadine,^{11,24-26} cetirizine,^{27,28} and loratadine,²⁹⁻³¹ the leukotriene receptor antagonist montelukast,²⁹⁻³¹ and the intranasal corticosteroid fluticasone propionate when used either on a regular basis³² or as needed.³³ Comparative studies have not revealed any differences in the magnitude of improvement between loratadine and montelukast,²⁹⁻³¹ whereas similar comparative studies have shown fexofenadine (Fig 2),¹¹ fluticasone³⁴—even when used on an as-needed basis—and triamcinolone acetonide³⁵ all to have significantly greater effect in improving RQLQ than treatment with loratadine. One comparative study of fluticasone and triamcinolone nasal corticosteroid sprays in SAR reported a comparable effect in improving RQLQ with both treatments.³⁶ Intervention with a new agent, anti-IgE (omalizumab), has also been shown to improve RQLQ scores in birch pollen-sensitive SAR (Fig 3).³⁷ It is thus apparent that the RQLQ is able not only to identify disease-related treatment effects but also to discriminate between different treatment modalities or reveal their comparable effects.

ASSESSMENT OF OLFACTORY FUNCTION

Although standard diary card recording of nasal symptoms assesses itch, sneeze, rhinorrhea, and obstruction, impairment of the sense of smell is rarely evaluated and is also largely ignored in consultations by the allergist and otorhinolaryngologist. This happens in spite of the fact that this primary sensory system commonly falls within their realm of practice, is essential for most of the flavor of foods and beverages, and serves as an early warning system for the detection of environmental hazards, including spoiled foods, leaking natural gas, smoke, and various airborne pollutants. Olfaction signif-

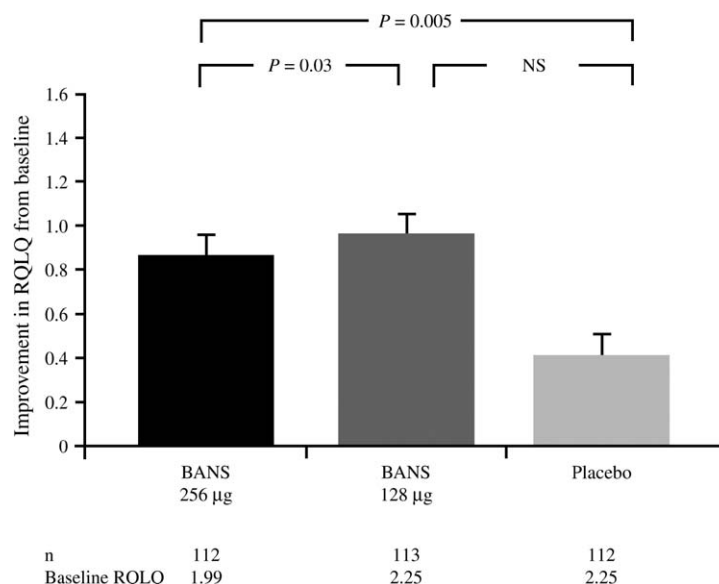


FIG 1. Improvement in RQLQ score with budesonide aqueous nasal spray (BANS) at 2 dose levels in comparison with placebo in perennial allergic rhinitis. *NS*, not significant. Adapted from Ståhl et al.¹³

icantly affects QOL, allowing the full appreciation of flowers, perfumes, spices, and the vast array of foods and beverages, as well as the seashore, the mountains, and the seasons of the year. Importantly, altered smell function can adversely influence food preferences, food intake, and appetite. Thus, it is no wonder that loss or distortion of smell sensation is of considerable significance to patients, particularly those dependent on this sense for their livelihood or safety (eg, cooks, homemakers, plumbers, fire fighters, perfumers, fragrance sales persons, wine merchants, food and beverage distributors, and employees of numerous chemical, gas, and public works industries).

Why measure sense of smell?

Quantitative olfactory testing is essential to (1) determine the validity of the patient's complaint, (2) characterize the specific nature of the problem, (3) reliably monitor changes in function over time (including the influences of medical or surgical interventions), (4) detect malingering, and (5) establish compensation for permanent disability. Although in the past, an astute physician might test the sense of smell by asking the patient to identify several crude odorants (eg, coffee, tobacco) placed under the nose, this approach commonly leads to the wrong conclusions, lacks reliability, is not quantifiable, has no normative reference, and is easily faked by malingerers. Procedures that blast odorants into the nose,³⁸ although seeming more quantitative, are unreliable and confound proprioceptive cues with the olfactory sensitivity measure.^{26,39} Such nonforced-choice paradigms also confound an individual's response criterion (eg, tendency to say yes under uncertain circumstances) with the measure of sensory sensitivity. Fortunately,

largely as a result of impetus from the National Institutes of Health in the United States, recent advances have been made in the development and application of easy-to-use and reliable tests of olfactory function applicable in clinical settings.

Basic methodological considerations in smell testing

The sense of smell can detect tens of thousands of odorants. Although accurate assessment of such a sense would at first glance seem daunting, in fact its function is easily measured. In part, this is because olfactory receptors are distributed more or less randomly throughout the olfactory epithelium, albeit with segregation into a few regional zones, and because damage to the epithelium generally affects cells that encode information for several molecules.⁴⁰ Damage to more central structures similarly influences pathways or centers that code information from more than 1 type of receptor cell. Hence, one needs to probe only a few well-chosen target odorants within an appropriate psychophysical paradigm to assess clinically the overall functioning of the system.

The utility of a sensory test depends on the degree to which it is reliable (consistent, dependable, stable), valid (measures accurately what it claims to measure), and practical (eg, able to be administered within a reasonable amount of time with little tester effort). Related to the validity of a test are its sensitivity (ability to detect abnormalities when present), specificity (ability to detect abnormalities with a minimum of false positives), and positive predictive value (the proportion of all positive test results that are true positives). A test's reliability can be determined in several ways. First and most commonly,

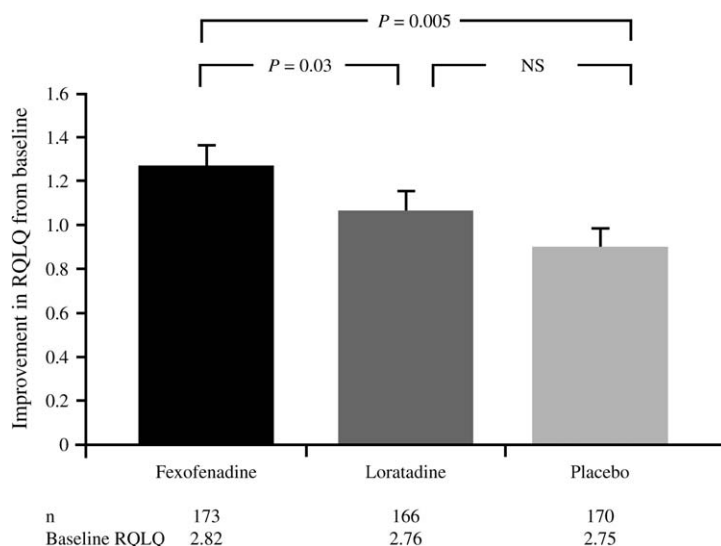


FIG 2. Improvement in RQLQ score with fexofenadine compared with placebo and loratadine in seasonal allergic rhinitis. NS, not significant. Reproduced with permission from Blackwell Publishing.¹¹

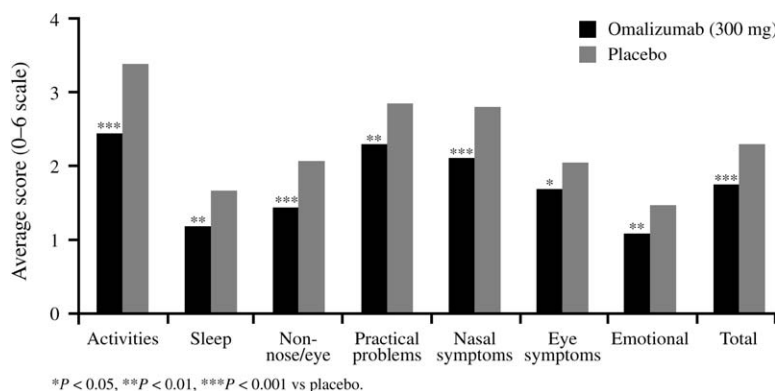


FIG 3. Improvement in individual QOL domains in seasonal allergic rhinitis with anti-IgE mAb therapy (omalizumab) in comparison with placebo. Adapted from Adelroth et al.³⁷

a given test (or alternate forms of the same test) is administered to the same set of individuals on 2 occasions, and a correlation coefficient is computed between the test measures on these occasions, providing an index of its test-retest reliability. Second, subsections of some types of tests (eg, a multiple-item odor identification test) can be inter-correlated to give an estimate of the test stability. In this case, the single test is viewed as consisting of parallel forms, and the resulting correlation coefficient is termed the *split-half reliability coefficient*. Because reliability is a function of test length, a mathematical correction is then applied to the correlation coefficient obtained in this way to obtain the correct reliability coefficient for the full-length test.⁴¹

Although several types of validity have been defined, some are difficult to quantify. The most common types of validity described in test measurement theory are content validity (the degree to which a test is made up of items, odorants, and so forth relevant to the task at hand) and criterion-related validity (the degree to which a test

correlates with criteria known to be associated with the trait to be measured). Criterion-related validity can be subdivided into 2 classes depending on whether the criterion information is available immediately (concurrent validity) or later (predictive validity). An example of concurrent validity would be the situation in which a new olfactory test is administered to a group of people known to have differing degrees of olfactory abilities as measured by another type of test, and a correlation is determined between the new test and the other criterion measure or measures. An example of predictive ability is the appreciation that loss of sense of smell may be an early feature of Alzheimer disease and Parkinson disease.

It is important to realize that a test can be highly reliable but not valid, because reliability is influenced by only unsystematic (ie, random) sources of error, whereas validity is influenced by both systematic (ie, directional) and unsystematic sources of error. This reliability is a necessary but not sufficient condition for validity.



FIG 4. UPSIT. This 40-odorant self-administered test consists of four 10-page booklets. Each page contains a different scratch-and-sniff scented strip and an associated multiple-choice question. Photo courtesy of Sensonics, Inc. © 2000 Sensonics, Inc.

Olfactory tests applicable in the office or clinical setting

During the last few decades, easy-to-use, reliable, and quantitative tests of olfactory function applicable in the office setting have become generally available to the clinician. Such tests have significantly increased our understanding of the sense of smell in human beings, including the influences of factors such as age, sex, exposure to toxic agents, and various disease states on its function. Among such tests are the 40-odor University of Pennsylvania Smell Identification Test (UPSIT; known commercially as the Smell Identification Test),^{42,43} the 12-odor Brief-Smell Identification Test (also known as the Cross-Cultural Smell Identification Test),⁴³⁻⁴⁵ the 3-odor Pocket Smell Test,^{46,47} the 12-item Odor Memory Test,^{47,48} an Odor Confusion Matrix Test,⁴⁹ the San Diego Odor Identification Test,⁵⁰ the Scandinavian Odor Identification Test,⁵¹ the Sniff n Sticks test,^{52,53} the Viennese Olfactory Test Battery,⁵⁴ an 8-odor identification test using polyester diskettes,⁵⁵ and several tests of odor threshold,⁵⁶ including the Toyota and Takagi (T&T) olfactometer test⁵⁷ and the Smell Threshold Test (STT).⁵⁸

Of these tests, measures of odor identification and detection threshold have become the mainstay of clinical evaluation, and their relevance to assessment of rhinological disorders is considered here. The reader is referred elsewhere to the numerous other clinical applications of these tests, particularly in neurology.^{59,60} There are 2 main approaches: a smell identification test such as the UPSIT, which has been administered in a clinical setting to nearly 200,000 patients over the period of the last 2 decades and is the most widely used means of quantitatively assessing the ability to smell; and a smell threshold test that uses a stimulus with minimal activity on the 5th cranial nerve, such as the rose-like odorant phenyl ethyl alcohol. These 2 approaches are explained in more detail.

UPSIT. The UPSIT (Fig 4) can test each side of the nose separately, is amenable to self-administration, uses norms based on nearly 4000 persons, and is available in English, French, German, and Spanish versions.^{42,43} This extremely reliable test (test-retest $r = 0.94$),⁴¹ derived from test measurement theory, focuses on the comparative ability of individuals to identify several odorants at the suprathreshold level. Physically, the test consists of 4 test

booklets, each 10 pages in length. A strip containing a microencapsulated odorant is located on the bottom of each page, just below a 4-alternative multiple-choice question. For a given item, the patient simply scratches open a microencapsulated label with a pencil tip, smells the label, and signifies the odor quality from the 4 alternatives provided. Even if no smell is perceived, a response is required (ie, the test is forced-choice). An answer column for each item is conveniently located on the back of each test booklet, and the subject's total correct score out of the 40 items is determined. This score is then compared with those from normal individuals of the same age and sex by using a normative table. In addition to indicating the level of absolute smell function (ie, normosmia, mild hyposmia, moderate hyposmia, severe hyposmia, total anosmia), a percentile rank for each age and sex group is provided. Malingering is detected on the basis of improbable responses. This UPSIT was the impetus for a massive smell function survey sent to nearly 11 million subscribers to *National Geographic Magazine* in 1986.⁶¹

Although numerous variants of this test are commercially available, including 3-item and 12-item versions, the UPSIT is the sine qua non for assessing the ability to smell and has become the gold standard for validating other olfactory measures. Major nonclinical findings of the last decade and a half, derived from the UPSIT, conclude that (1) women, on average, have a better sense of smell than men (Fig 5), and this superiority is noticeable as early as 4 years of age and is culture-independent^{45,62,63}; (2) there is a substantial genetic influence on the ability to identify odors^{63,64}; (3) major loss of olfactory function occurs after the age of 65 years, with more than 1/2 of those between 65 and 80 years of age and more than 3/4 of those 80 years and older having such loss^{45,65,66}; (4) women, on average, retain the ability to smell longer than men⁶⁷; (5) the decrement in olfactory function associated with smoking is present in past smokers, and recovery to presmoking levels, although possible, can take years, depending on the duration and amount of past smoking⁶⁸; and (6) olfactory function is compromised in urban residents and in workers in some industries, including the paper and chemical manufacturing industries.⁶⁹⁻⁷⁵

Detection smell threshold testing. Two psychophysical procedures for presenting stimuli in detection threshold paradigms have received the most clinical use in the last 2 decades: (1) the ascending method of limits procedure (AML) and (2) the single staircase procedure (SS). In the AML procedure, an odorant is presented sequentially from low to high concentrations, and the point of transition between no detection and detection is estimated. In the SS method, the concentration of the stimulus is increased after trials in which a subject fails to detect the stimulus and decreased after trials in which correct detection occurs. An average of 4 or more up-down transitions (reversals) is used to estimate the threshold value. In both the AML and SS procedures, the direction of initial stimulus presentation is made from weak to strong in an effort to reduce potential adaptation effects of previous stimulation. The

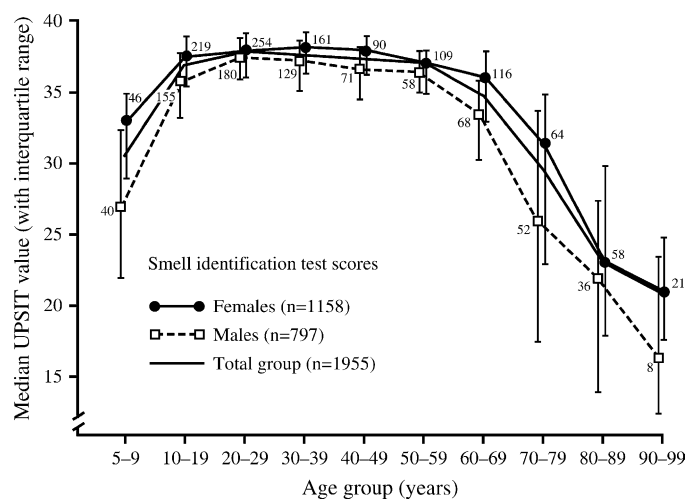


FIG 5. Change in olfactory test scores with the UPSIT according to sex and age.

AML procedure is generally less reliable than the SS procedure, largely because fewer trials are involved in establishing the estimate of threshold.

It has been generally believed that in the human being, sensitivity to odors, as measured by threshold techniques, exhibits considerable day-to-day variability. For example, one study of 60 subjects reported that intersubject variation was as great as 5 log units.⁷⁶ Another study reported intersubject variation in the order of 16 log units.⁷⁷ Stevens et al⁷⁸ obtained 60 threshold values over the course of 30 days from 3 subjects (20 for butanol, 20 for pyridine, and 20 for β -phenyl-ethylmethylethylcarbinol). The intrasubject variability across test days was found to be as great as intersubject variability on a given test day, suggesting to these authors that the large individual differences observed in threshold values are a reflection not of big differences among stable threshold values of subjects but of large day-to-day fluctuations in the test measures. Unfortunately, these studies used the relatively unreliable AML procedure to establish the thresholds, accounting for much of the reported variability. Cain and Gent,⁷⁹ in a study of 32 subjects, found that the correlation between single ascending series butanol thresholds determined for the left and right sides of the nose (which they used as their reliability measure) was at best 0.68 and as low as 0.30 when the butanol threshold was the first in a series of 4 threshold tests. Heywood and Costanzo⁸⁰ reported test-retest reliability coefficients for the same butanol threshold procedure on the left and right sides of the nose of 16 subjects to be 0.45 and 0.08, respectively, whereas Hummel et al⁵³ found the test-retest reliability of this test in 104 subjects to be 0.36. In contrast, thresholds determined by using the SS procedure exhibit reliability coefficients above 0.80, with the reliability coefficient predictably related to the number of staircase reversals included in the threshold measure.⁴⁷

One well-validated SS procedure is the phenyl ethyl alcohol (PEA) detection threshold test, commercially

termed the Smell Threshold Test. Physically, the STT (Fig 6) is composed of 17 high-density propylene squeeze bottles that contain concentrations of PEA ranging from -10.00 to -2.00 $\log_{10}$ units in half-log steps, and 4 blank bottles. These bottles are housed in a 2.7-kg aluminum carrying case that serves as a test table and contains a calculator (for computing geometric means), a clipboard writing surface, a response form tablet, a thermometer for ensuring exacting testing conditions, and a roll of tape for occluding the contralateral naris during unilateral testing. Liquids per se are not present in the bottles because the odorants are embedded in an absorbent material. In contrast with the round plastic squeeze bottles that have been used in some studies to present odorants to human subjects,^{56,81} this test kit uses oval squeeze bottles. Such bottles provide a more consistent stimulus over trials and a haptic and visual indication of the angular orientation of their spouts relative to the naris being tested, allowing for a more standardized stimulus presentation. The STT provides a reliable (test-retest $r=0.88$) and standardized means for assessing sensitivity to PEA, an odorant with a rose-like smell at higher concentrations and little or no intranasal trigeminal nerve reactivity.⁸² Versions of this test have been used at the University of Pennsylvania Smell and Taste Center and elsewhere over the course of nearly 2 decades.^{42,47,83-91}

Relationships among olfactory tests

In general, most tests of olfactory function correlate with one another.⁹² Such associations are often moderate, however, limited by the less reliable measure. One study found the correlation between the UPSIT and the PEA threshold test to be -0.79 .⁴² In a more recent study of 97 subjects, the relationship between the UPSIT and the PEA threshold test was -0.63 ($P < 0.001$). The latter study likely had a more attenuated range of test scores than the former study because none of the subjects complained of olfactory dysfunction, unlike in the former study.



FIG 6. STT. Concentrations of PEA, ranging from 10^{-2} to 10^{-10} log vol/vol in half-log concentration steps, are provided, along with blanks for forced-choice testing. Photo courtesy of Sensonics, Inc. © 2000 Sensonics, Inc.

Nonetheless, the 0.63 coefficient was considerably higher than those between the UPSIT and other threshold measures, including the single ascending butanol threshold ($r = 0.43$), the single ascending phenyl ethyl methyl ethyl carbinol threshold ($r = 0.29$), and the T&T olfactometer identification and detection composites ($r = 0.21$ and 0.24 , respectively).⁹²

Clinical applications of olfactory test methods

Although some olfactory disorders are reversible, many are not, and iatrogenic causes of smell dysfunction are not uncommon. Thus, numerous medications adversely influence the ability to smell, including some nasal sprays, chemotherapeutic agents, antidepressants, antibiotics, antihypertensive drugs, and lipid-controlling agents.⁹³ Smell loss can be a very early sign, perhaps the earliest sign, of Alzheimer disease and idiopathic Parkinson disease.⁶⁰ Because many patients are unaware of mild olfactory losses, it is incumbent on physicians to assess olfactory function accurately and quantitatively in their patients. Such testing is not a trivial matter, because early diagnosis of Alzheimer disease and Parkinson disease, for example, can increase the efficacy of drugs that delay or mitigate the expression of disease symptoms.

Several studies have used either the UPSIT or PEA detection thresholds for assessing the influences of nasal airway blockage, nasal disease, or medical or surgical procedures for correcting nasal or olfactory function.

It is interesting that although several such studies find a general association between the degree of smell loss and nasal disease severity, no relationship is apparent between airway patency (eg, measured by rhinomanometry) and olfactory dysfunction, except when marked obstruction is present. Furthermore, on average, objectively measured smell function rarely returns to normal in patients with rhinosinusitis, polyposis, or other forms of nasal disease, even after systemic corticosteroid treatment or nasal surgery, including endoscopic nasal sinus surgery. Such

findings support the view that factors other than or in addition to, nasal airflow are responsible for many instances of smell loss in patients with rhinosinusitis, in accord with the notion that chronic inflammation may be toxic to olfactory neurons.⁹⁴ Kern⁹⁵ has presented data suggesting that the severity of histopathological changes within the olfactory mucosa of patients with chronic rhinosinusitis is positively related to the magnitude of olfactory loss, as measured by the UPSIT. Feron et al⁹⁶ reported in a study group of 33 subjects that nasal biopsies from the posterior superior turbinate, posterior medial turbinate, and posterodorsal septum of patients with nasal disease were less likely to contain olfactory neuroepithelium than analogous biopsies from patients with no such disease. Lee et al⁹⁷ have demonstrated that biopsies from the region of the olfactory epithelium of anosmic patients with rhinosinusitis were less likely to contain olfactory epithelial tissue than those from rhinosinusitis patients who were not anosmic (27% vs 61% positive biopsies, respectively). Although detailed examination by Lee et al⁹⁷ of the epithelium from rhinosinusitis patients with normal smell function still revealed islands of respiratory-like epithelium interspersed throughout the biopsy samples, such islands were much less prevalent than in the anosmic patients for whom olfactory epithelium could be found. Abnormalities in the arrangement of the epithelial cell types were common in the anosmic biopsies, and in cases in which olfactory epithelium was identified, it was typically atrophic and thin, often composed mainly of sustentacular cells and basal cells. Clearly, the bulk of the histological studies imply that rhinosinusitis-related olfactory loss is not caused solely by decreased airflow to the olfactory epithelium, and that steroid-related influences on olfactory function, when in fact present, reflect influences on the olfactory epithelium in addition to altering upper nasal airway patency.

In conclusion, although associations have been observed between the degree of smell loss and the severity of nasal disease, no relationship appears to be present between airway patency and olfactory dysfunction except in cases of severe blockage. This observation, along with histopathological data and the lack of strong efficacy of medical and surgical interventions, suggests that airflow access is not the sole determinant of the smell loss of such patients. Although the weight of evidence suggests that nasal steroids, when appropriately administered, can improve olfactory function in some patients, this is clearly not the case in all. Surprisingly, despite the availability of defined methods for the measurement of olfactory function, no double-blind placebo-controlled studies with objective monitoring have evaluated the efficacy of corticosteroids in restoring smell function.

MONITORING ADVERSE EFFECTS OF SPECIFIC THERAPIES IN RHINITIS

In addition to monitoring beneficial outcomes in clinical trials, it is also necessary to monitor any adverse

outcomes. This is done on an open basis with recording of any patient-reported life events during the trial period and, depending on the half-lives of interventions in therapeutic studies, often during a follow-up period after cessation of trial intervention. In addition to the subjective reporting, there is objective measurement of cardiac parameters such as pulse rate and blood pressure; blood testing of hematological, hepatic, renal, and other biochemical indices, such as glucose and lipids; and possibly also urine testing. Additional investigations may be undertaken to assess specific potential adverse effects, as indicated either by previous experience or on the basis of known pharmacology. The basis and conduct of such additional assessments will be specifically considered in relationship to H₁-antihistamines and intranasal steroids, the 2 most common classes of therapy used in the treatment of rhinitis.⁹⁸

H₁-antihistamines

H₁-antihistamines, used ubiquitously for almost 60 years in the treatment of allergic rhinoconjunctivitis, differ considerably in their safety profiles.^{99,100} Central nervous system (CNS) and cardiac toxicity have been the most serious adverse effects associated with H₁-antihistamines. Cardiac toxicity is extremely rare but causes considerable concern because of the potential lethality of such an occurrence. Fortunately, the understanding of the mechanisms behind both these adverse effects of H₁-antihistamines is now much greater and has led to *in vitro* models to screen compounds under development.

The CNS toxicity produced by first-generation H₁-antihistamines is widespread and underrecognized. In studies involving as few as 6 participants, statistically significant and clinically relevant differences between a first-generation sedating H₁-antihistamine and a second-generation nonsedating H₁-antihistamine can be demonstrated by using a battery of selected subjective and objective tests and a prospective, randomized, double-blind, placebo-controlled, crossover study design. In contrast, even during the years when astemizole and terfenadine were widely used, case reports of cardiac toxicity were uncommon, and epidemiological studies in hundreds of thousands of users identified only a small number with H₁-antihistamine-associated ventricular arrhythmias. Because allergic rhinoconjunctivitis itself never causes fatalities, the benefit-to-risk ratio of each H₁-antihistamine used for the treatment of this disorder should be scrutinized carefully. Physicians should recommend only H₁-antihistamines with an excellent safety record. Fortunately, several second-generation H₁-antihistamines devoid of any cardiac toxicity and free from significant CNS toxicity are now available for use worldwide and are the H₁-antihistamines of choice. CNS effects of these drugs have been evaluated for the most part in healthy control volunteers rather than in individuals with allergic rhinitis, in whom H₁-antihistamines are most widely used. In cancer patients, the elderly, pregnant women, infants, and children, there are special considerations with regard to H₁-antihistamine safety.

CNS adverse effects. In the brain, histamine, acting at H₁-receptors, plays an important role in neurotransmission, particularly with regard to processing of sensory inputs and cognition. Confirmation of this comes from molecular biology studies: in H₁-receptor knockout mice with targeted disruption of the H₁-receptor gene, histamine no longer functions as a neurotransmitter. Learning, memory, behavior, and locomotion are affected, and electrically induced convulsions are prolonged.¹⁰¹

In human beings, most first-generation, potentially sedating H₁-antihistamines readily penetrate the blood-brain barrier consisting of nonfenestrated capillaries with tight endothelial junctions, pericytes, and astrocytes. The CNS effects of first-generation H₁-antihistamines are mediated primarily by blockade of the neurotransmitter effect of endogenous histamine, as confirmed by the discovery that the sedative enantiomers of chlorpheniramine and dimethindene are those with the highest H₁-receptor affinity.¹⁰² Blockade of the effects of acetylcholine, serotonin, and other amine neurotransmitters may also be a contributing factor, because in addition to their CNS effects, these old H₁-antihistamines may cause anticholinergic effects (dry mouth and mucous membranes, difficulty in micturition, impotence, tachycardia, and constipation), and some cause antiserotonin effects resulting in, for example, appetite increase and weight gain.^{99,100}

CNS adverse effects of first generation H₁-antihistamines. Even at low doses, such as chlorpheniramine at 1 to 2 mg, first-generation sedating H₁-antihistamines occupy 70% to 100% of the H₁-receptors in the frontal, temporal, and anterior cingulate cortices, as measured by using radiolabeled H₁-antihistamines, positron emission tomography (PET), or magnetic resonance imaging (MRI).¹⁰²⁻¹⁰⁶ At doses used in the treatment of allergic disorders, H₁-antihistamines frequently cause somnolence, sedation, drowsiness, fatigue, and impaired concentration and memory.^{99,100} These adverse CNS effects were recognized soon after clinically useful H₁-antihistamines such as diphenhydramine and tripeleminamine were introduced in the 1940s. The incidence of subjectively reported somnolence varies depending on the first-generation H₁-antihistamine ingested, ranging from 40% after chlorpheniramine or brompheniramine to 80% after hydroxyzine.¹⁰⁷ Some individuals deny subjective adverse effects despite objective evidence of impairment—that is, lack of drowsiness does not mean that an individual will be able to drive a vehicle without impairment.¹⁰⁸ In contrast, other individuals complain of somnolence, yet are able to perform psychomotor tests adequately. Additional clinically relevant concerns about CNS symptoms from first-generation H₁-antihistamines are listed in Table I.

A detailed description of measurement of the CNS effects of H₁-antihistamines is given in Table II.¹⁰⁹⁻¹¹⁵ Because the sensitivity of objective tests used to measure CNS impairment after medication intake differs, a variety of tests are used, and both a positive control (sedating H₁-antihistamine) and a negative control (placebo) are

TABLE I. CNS symptoms from old, sedating, first-generation H₁-antihistamines

Impairment is produced even by low doses (eg, chlorpheniramine 4 mg, diphenhydramine 25 mg, promethazine 10 mg, triprolidine 5 mg)
Effects are similar to and additive with those produced by alcohol (ethanol) or other CNS-active medications
Some patients are especially vulnerable (eg, female subjects, the elderly, persons with small body mass, hepatic/renal dysfunction, allergic rhinitis, or pre-existing CNS disorder)
Tolerance to sedation and psychomotor impairment does not necessarily develop
Bedtime dosing may not decrease daytime CNS functional impairment (also known as an antihistamine hangover)
Concomitant use of a CNS stimulant (eg, a decongestant such as pseudoephedrine) may not decrease CNS functional impairment; the sedation usually predominates
Paradoxical CNS symptoms (eg, seizures, dyskinesia, dystonia, or hallucinations) may occur in young children even after recommended doses

generally incorporated into the study design. By using a battery of selected subjective and objective tests and a prospective, randomized, double-blind, placebo-controlled, crossover study design, statistically significant and clinically relevant differences between a sedating H₁-antihistamine and a nonsedating H₁-antihistamine can be demonstrated in studies involving as few as 6 participants.¹¹⁵

The CNS functional impairments produced by the sedating, first-generation H₁-antihistamines are so common that these medications are not approved for use by military and commercial pilots.^{115,116} In other professions and occupations, they continue to be implicated as a cause of accidents, injuries, and suboptimal work performance.¹¹⁷ In schools and other educational settings, they may contribute to learning impairment.¹¹⁸

Assessment of CNS adverse effects of second-generation H₁-antihistamines. Second-generation H₁-antihistamines such as cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and mizolastine do not cross the blood-brain barrier as readily as their predecessors do. Those that have been tested by using radiolabeling and PET or MRI appear to occupy fewer than 30% of H₁-receptors in the frontal, temporal, and cingulate cortices.^{103,104,119}

At manufacturers' recommended doses, the relatively nonsedating second-generation H₁-antihistamines are less likely to slow neurotransmission, cause somnolence, or impair psychomotor performance than their first-generation predecessors. Their CNS effects can be differentiated readily from those of the first-generation medications by using the objective psychomotor tests and electroencephalograms described in Table II.

There are few direct comparative studies among these medications; however, within the designation *second-generation H₁-antihistamines*, some appear to be more sedating than others.^{112,114,120} This is especially true if the

TABLE II. Measurement of CNS effects of H₁-antihistamines in human beings

Mechanism: interference with neurotransmitter effect of histamine in the CNS
Subjective: symptoms of somnolence, sedation or fatigue as assessed using scores, visual analogue scales, or standardized questionnaires
Objective tests: psychomotor performance; electroencephalogram (multiple sleep latency test, P-300–event-related potential, 24-hour electroencephalogram), PET scanning, MRI
Objective measurements correlate well with each other
Subjective and objective measurements do not correlate perfectly with each other
Significant change: depends on test; usually 25% > placebo
Dose/test time relationship:
Strongest 2–4 h postdose at time of peak plasma H ₁ -antihistamine concentrations
Can be documented 1.5–24 h postdose
Many studies involve a single test time postdose, and few studies last longer than 8 hours
Ease of measurement: variable; ranges from simple subjective score to complex tests involving ingestion of radiolabeled H ₁ -antihistamines, unlabeled H ₁ -antihistamines, and PET scanning
Reproducibility: variable; highest with subjective scores and lowest with electroencephalograms
Sources of variation: time of day, previous experience with psychomotor test (practice)
Intrinsic confounding factors: age, sex, CNS disorders (either diagnosed or subclinical), intelligence, memory, coordination, motivation, boredom
Extrinsic confounding factors: other CNS-active medications, caffeine, alcohol (ethanol)
Number needed to measure symptoms (somnolence): 6 per group
Performance (battery of tests/simulator driving or flying/actual driving): 6 per group
Electroencephalogram (multiple sleep latency test): 6 per group
Tests vary from readily available (subjective scores) to unavailable in most countries (eg, PET scans and MRIs for research purposes, on-road driving tests)
Additional issues:
Most studies have been performed in
Healthy volunteers and do not include the effect of the allergic rhinoconjunctivitis itself on CNS function
Adults age 18–65 y
Reporting of results as mean values, $\pm$ SD, or $\pm$ SEM, obscures results in outliers

recommended dose is exceeded. In animal studies, passive membrane permeability, p-glycoprotein efflux, and plasma protein binding have been shown to influence the access of antihistamines to central H₁-receptors.¹²¹ P-glycoprotein is a transporter protein present in the vascular endothelium and prevents molecules, including H₁-antihistamines, from access to the CNS by actively transporting them back into the vascular compartment.¹²² Whether medications are a substrate for p-glycoprotein is increasingly being appreciated as an important determinant of the central potential of H₁-antihistamines.^{123,124} Consistent with this, fexofenadine is an excellent substrate for p-glycoprotein,¹²⁵ and this antihistamine appears to be

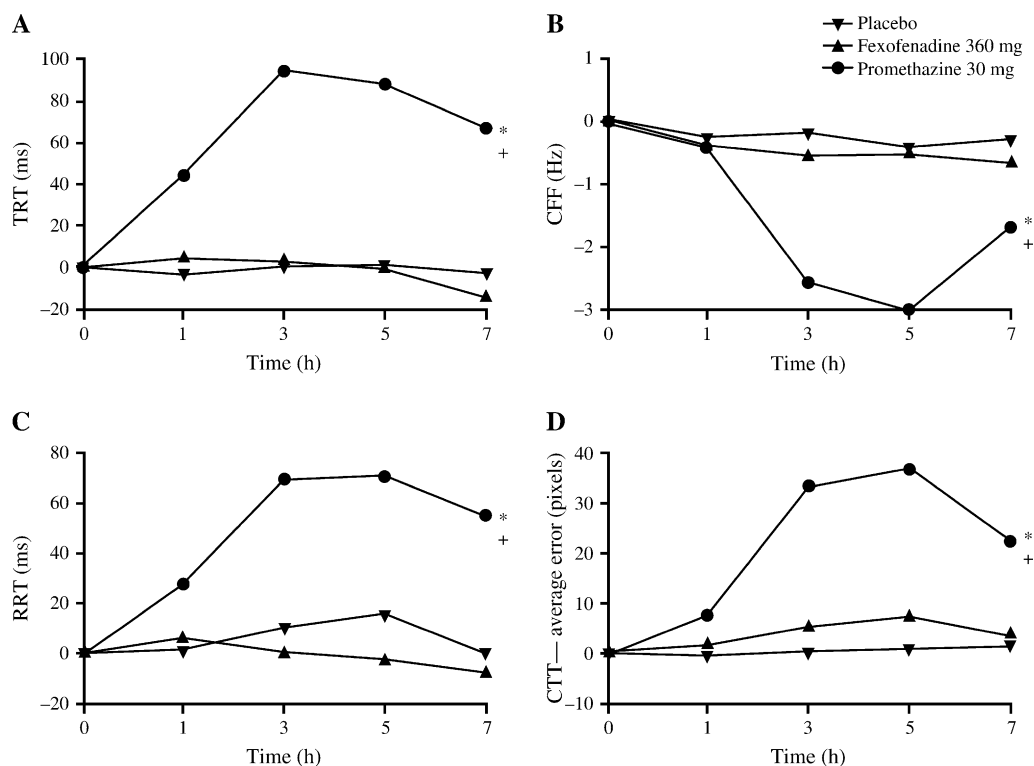


FIG 7. Lack of effect of fexofenadine 360 mg administered at 3 times the standard clinical dose for allergic rhinitis on a range of objective outcome measures of CNS psychomotor function in comparison with placebo and an active control, promethazine 30 mg. Impairment was seen with the active control in 15 subjects in (A) total reaction time (TRT), (B) critical flicker fusion (CFF), (C) recognition reaction time (RRT), and (D) compensatory tracking task (CTT). * $P < 0.05$ versus placebo. * $P < 0.05$ versus fexofenadine. Reproduced with permission from Blackwell Publishing.¹²⁶

relatively free from any CNS effects over a wide range of doses,¹¹⁵ even when studied at 360 mg, which is 3 times the standard dose used for allergic rhinitis (Fig 7),¹²⁶ and to be devoid of central H_1 -receptor occupancy on PET scanning.¹¹⁹

Cardiac toxicity

Adverse cardiovascular effects of first-generation H_1 -antihistamines. In large doses or overdoses, old H_1 -antihistamines such as diphenhydramine may be associated with prolonged QT interval corrected for heart rate (QTc) and cardiac arrhythmias.¹²⁷

Adverse effects of second-generation H_1 -antihistamines: Not a class effect. Astemizole and terfenadine, which are no longer approved by regulatory agencies in most countries because of their potential to cause serious ventricular arrhythmias such as torsades de pointes, have provided important lessons about the potential cardiac toxicity of H_1 -antihistamines. Individuals with ventricular arrhythmias present with symptoms such as syncope at rest or on exercise, dizziness, loss of consciousness, and palpitations. Factors that increase the risk of H_1 -antihistamine-induced cardiac toxicity are listed in Table III.¹²⁸⁻¹³¹

The chief mechanism underlying the cardiac toxicity of H_1 -antihistamines is blockade of the potassium channels

involved in action potential repolarization in the ventricular myocardium—in particular, blockade of the rapidly activating component of the delayed rectifier K^+ current (IKr) component of the cardiac repolarizing current. The slowly activating component of the delayed rectifier K^+ current (IKs) and inward rectifier component of the delayed rectifier K^+ current (IKi) channels, which are expressed to different degrees in different individuals, may also be involved. Blockade of potassium channels leads to prolongation of the monophasic action potential (QT interval on the surface electrocardiogram). This may then induce the development of early after-depolarizations and dispersion of repolarization, leading to torsade de pointes through re-entry mechanisms.¹³⁰⁻¹³² Clinical evidence of cardiac toxicity of H_1 -antihistamines (torsade de pointes and other ventricular arrhythmias) is extremely rare,^{128,133} in contrast with the near-ubiquitous CNS adverse effects of the first-generation H_1 -antihistamines. Astemizole and terfenadine were used for many years in hundreds of thousands of patients before their adverse cardiac effects became apparent. In one pharmacoepidemiology study involving approximately 600,000 patients, life-threatening ventricular arrhythmias and cardiac arrest were actually more frequent in the cohort of patients receiving diphenhydramine and other first-generation H_1 -antihistamines than in the cohorts taking terfenadine,

TABLE III. Measurement of cardiac effects of H₁-antihistamines in human beings

Mechanism: blockade of ion channels, especially the IKr channel, in the ventricular myocardium
Subjective: symptoms of fainting at rest or with exercise, loss of consciousness, palpitations
Objective tests: electrocardiogram (significant change in QTc interval is a value of >440 ms (men) and >460 ms (women); a QTc interval of >500 ms suggests a strong likelihood of a drug effect; an increase in QTc of ± 35 ms while receiving an H ₁ -antihistamine is likely to represent a drug effect (95% CI), as does the ventricular arrhythmia torsades de pointes
Subjective symptom and objective test correlations: patients with QTc interval prolongation are asymptomatic; however, in torsade de pointes, the symptoms and the electrocardiogram correlate
Dose and test time relationships are not well defined; the thousands of electrocardiograms performed during clinical trials have generally been performed before the first dose of the H ₁ -antihistamine and at steady state after at least a week of regular daily dosing
Ease of measurement: good (electrocardiograms are readily available)
Reproducibility: good (for electrocardiograms)
Sources of variation:
Skill of technician
Lead placement
Number of leads (ideally 12)
Paper speed (ideally 50 mm/s)
Amplitude (ideally 0.5 mV/km)
Sensitivity and specificity of interpretation (computer program or cardiologist)
Correction factor used for rapid heart rate (eg, Bazett, Fridericia, Hodge, Lécocq)
Intrinsic confounding factors: age, sex, electrolyte (K ⁺ , Ca ⁺⁺ , Mg ⁺⁺) abnormalities, pre-existing electrocardiogram abnormalities, eg, long QT syndrome or systemic diseases (hepatorenal, cardiovascular, cerebrovascular)
Extrinsic confounding factors: concurrent medications: other H ₁ -antihistamines (astemizole/terfenadine*), H ₁ -antihistamine overdose, antimicrobials (macrolide antibiotics and imidazole antifungals), antimalarials, antiarrhythmics, calcium channel blockers, psychiatric drugs, serotonin agonist and antihistamines, immunosuppressants (tacrolimus), antidiuretic hormone (vasopressin) and other agents (eg, cocaine)
Additional issue: reporting of results as mean values, $\pm$ SD, or $\pm$ SEM, obscures results in outliers; therefore, ranges should also be given

*No longer approved by FDA but still available in some countries.

clemastine, or ibuprofen, the negative controls (Fig 8).¹²⁸ The epidemiologic techniques used in this study were sensitive enough to identify evidence of a terfenadine-erythromycin interaction.

In another pharmacoepidemiologic study performed in 198,000 patients from 1992 to 1996, prescription of astemizole, terfenadine, and other nonsedating antihistamines was found to increase the risk of ventricular arrhythmias by a factor of 4 in the general population.¹³¹ The absolute effect was extremely low, however, requiring 57,000 prescriptions or 5300 person-years of use for 1 case of ventricular arrhythmia to occur.¹³³ The epidemiological techniques used in this study identified

2.7% of antihistamine prescriptions as high-dose and 3.4% of prescriptions involving overlap with other medications such as the cytochrome P450 inhibitors erythromycin or itraconazole.

A large population of users was necessary to identify the cardiac risks from astemizole or terfenadine. Nevertheless, because allergic rhinitis is not a life-threatening disorder, the medications used to treat it should have an excellent safety profile, and appropriately, most regulatory agencies worldwide have withdrawn approval for astemizole and terfenadine. Despite this, these medications have not yet disappeared completely, even in countries where they have not been legitimately sold for several years, because patients may use old supplies or obtain them from nontraditional or offshore sources.¹³⁴

All new H₁-antihistamines are now studied *in vitro* and in animal models for cardiotoxic potential before being administered to human beings.^{130,131,135-137} One useful screening test is based on their ability to block the potassium channel encoded by the human ether-a-go-go-related gene in *Xenopus* oocytes, which represents the molecular basis of the IKr channel.^{132,138} Because there is no correlation between human ether-a-go-go-related gene blockade/cardiotoxic potential and H₁-antihistamine activity, the cardiotoxic effects of H₁-antihistamines are not a class effect.

After the *in vitro* studies and the animal studies, thorough and systematic investigation of the potential cardiac toxicity of H₁-antihistamines is conducted in thousands of patients. Measurement of cardiac effects of H₁-antihistamines in human beings is summarized in Table III.^{129-131,139,140} Prospective clinical studies involve repetitive escalating doses, potential drug interactions, long-term daily administration, and postmarketing surveillance. In these studies, the second-generation H₁-antihistamines cetirizine, fexofenadine, and loratadine appear to be free from cardiac toxicity. Furthermore, in widespread use, including use on a nonprescription basis in many countries, there are no confirmed reports of arrhythmias associated with these medications, either after recommended doses or after overdose.

Other second-generation H₁-antihistamines such as acrivastine, azelastine, ebastine, levocabastine, and mizolastine, and the newest H₁-antihistamines carebastine, desloratadine, and levocetirizine, also appear to have a negligible potential for cardiac toxicity at standard doses. The term *third-generation* has been introduced to mean absence of cardiovascular activity. However, because it is also used to refer to other attributes of H₁-antihistamines, including total absence of CNS toxicity even at supratherapeutic doses,¹¹² unique pharmacokinetic properties, antiallergic/anti-inflammatory activities, and other concepts, this terminology is best avoided.

Special populations

Cancer patients. H₁-antihistamines have been reported to restore sensitivity to multidrug-resistant cancer cells *in vitro* by inhibition of the p-glycoprotein transporter function and intracellular accumulation of antineoplastic

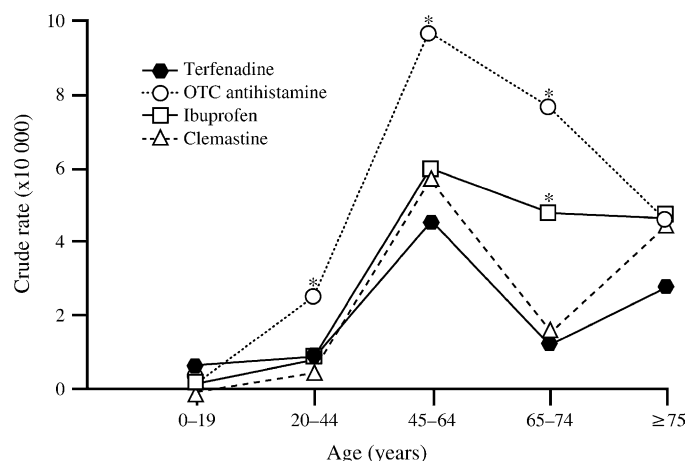


FIG 8. Influence of age and therapy on crude rates per 10,000 for life-threatening ventricular arrhythmias and cardiac arrest within the population. * $P < 0.05$ versus terfenadine. OTC, over the counter. Reprinted with permission from Pratt et al. *Excerpta Medica*. © 1994.¹²⁸

medications. Large epidemiological studies of the long-term safety of H₁-antihistamines have not raised any concerns about their potential tumor-promoting effects,¹⁴¹⁻¹⁴³ and case reports of tumor promotion in this population are extremely rare. In mice, some H₁-antihistamines injected by the intraperitoneal route were reported to promote the growth of B16F10 melanoma cells or C-3 fibrosarcoma cells injected subcutaneously¹⁴⁴; however, these findings have not been replicated, and regulatory agencies have not recommended any change in H₁-antihistamine usage on the basis of them.

Elderly patients. Pre-existing disorders are common in this population and include subclinical dementia,¹⁴⁵ overt CNS disorders such as Alzheimer disease,¹⁴⁶ cerebrovascular disease, cardiovascular disease, and age-related or disease-related reduction in hepatic or renal function. Polypharmacy and potential for drug-drug interactions are also common in the elderly. All of these problems increase the risk of toxicity from CNS-active medications. There are few objective studies of the CNS effects of older H₁-antihistamines in the elderly,¹⁴⁷ and interpretation of CNS toxicity data in this population is challenging because of the factors described. Pre-existing disorders and polypharmacy also increase the susceptibility of elderly people to cardiac toxicity from H₁-antihistamines.^{128,133} Many of the patients experiencing torsade de pointes during astemizole or terfenadine treatment were in their 60s or older.

Pregnancy. All H₁-antihistamines cross the placenta, and some are teratogenic in animals. Most H₁-antihistamines are classified by the US Food and Drug Administration (FDA) as pregnancy category C and should be used during pregnancy only if the expected benefits to the mother exceed the unknown risks to the fetus. A few, such as cetirizine and loratadine, are classified as lower-risk pregnancy category B.^{148,149} Although the first-generation H₁-antihistamines chlorpheniramine and triproleamine are deemed to be relatively safe for use in pregnancy (FDA category B), on the basis

of large retrospective epidemiologic studies involving several hundred thousand women and their newborns, the second-generation H₁-antihistamines cetirizine and loratadine, which are also FDA category B, should be used in preference for allergic rhinitis treatment. Prospective, controlled, observational studies of women taking H₁-antihistamines during the first trimester of pregnancy are now being performed, although to date, the numbers of mothers and infants in these databases are small. The relative safety of H₁-antihistamines in pregnancy is confirmed in large, retrospective epidemiological studies involving several hundred thousand women and their newborns.^{100,148,150}

Infants and children. In infants under 12 months of age, published data regarding H₁-antihistamine safety are scarce. In the past, use of old H₁-antihistamines, especially the phenothiazines, has been linked with sudden infant death syndrome. Until the appropriate safety studies are performed in infants, H₁-antihistamines should be used with extreme caution in this population, although reassuringly, a recent randomized, placebo-controlled, parallel group study of cetirizine (0.25 mg/kg twice a day for 1 week) in 85 infants age 6 to 11 months found no significant adverse effects, and in particular, objective monitoring of electrocardiograms in this population revealed no conduction abnormalities related to this specific treatment.¹⁵¹

In more than 800 toddlers, cetirizine (0.25 mg/kg twice a day) has been found to be safe in an 18-month long, randomized, placebo-controlled, double-blind study.¹⁵² A further report from this Early Treatment of the Atopic Child study detailed results of well-validated and standardized measures of behavior (Behavior Screening Questionnaire) and cognition (McCarthy Scales of Children's Abilities) as well as the ages of attainment of psychomotor milestones.¹⁵³ These measures were applied between the ages of 32 and 53 months, both during the study treatment with cetirizine or placebo and after the study treatment had been discontinued. The Behavior

Screening Questionnaire was completed at least once on approximately 300 children in each group and on approximately 200 children on 5 occasions. The McCarthy Scales of Children's Abilities were administered to approximately 100 in each group at 3 different times. There were no significant differences between the cetirizine and placebo groups in either of the behavior and cognition measures or in psychomotor milestones during or after the study treatment. These findings suggest that there are no adverse effects on behavior or learning processes associated with the prolonged use of cetirizine in young children with atopic dermatitis.

In hundreds of children age 4 to 11 years with allergic rhinoconjunctivitis, subjective safety data about second-generation H₁-antihistamines have been obtained during prospective clinical trials as long as 6 weeks. In a few short-term pediatric studies, objective performance measurements or electroencephalograms have been recorded in 15 to 25 children (crossover studies)^{154,155} or approximately 60 children each (parallel-group studies).¹⁵³ Measurement of P-300–event-related potential by scalp electrode monitoring in children has identified in crossover studies that whereas terfenadine has no effect,¹⁵⁴ that both cetirizine¹⁵⁵ and chlorphiramine¹⁵⁴ increased the latency of recording. P-300–event-related potential is an index of cognitive ability, and such an increase is a reflection of impaired cognitive ability. This defect was not reflected in subjective visual analogue scoring and indicates that children are poor perceivers of CNS impairment with H₁-antihistamines.

Assessing the systemic effects of intranasal steroids

Intranasal steroids (INSs) have well-documented efficacy in the treatment of allergic rhinitis compared both with placebo and antihistamines.¹⁵⁶⁻¹⁵⁹ The sparsity of reported adverse events, despite the extensive use of INS over many years, suggests that the clinical safety of these medications is already well established.¹⁶⁰⁻¹⁶⁴ This does not mean, however, that there should not be an awareness of the potential for adverse systemic effects of INS. The comfort factor with this treatment has led to more consistent and more prolonged use. In younger and older patients, in whom mild degrees of cortisol excess could have important effects on growth or bone metabolism, this could have important implications. Furthermore, the more widespread use of local steroid administration for allergic disease suppression is associated with administration to multiple sites. Thus, INS-treated patients may also be receiving inhaled corticosteroid (ICS) or other topical corticosteroid treatment. Under such circumstances, an additive systemic steroid burden may become significant. The contribution of INS to this will depend on systemic bioavailability after nasal administration.⁹⁸ Both local bioavailability from the nose, in association with the abundant vascularity of the nasal mucosa, and bioavailability from the gut, resulting from the significant swallowed fraction,^{98,165} are important determinants of this potential for systemic bioavailability. The first-pass

metabolism of the corticosteroid molecule at both these sites determines the fractional absorption. Currently used INS corticosteroids vary significantly in the extent to which they undergo first-pass metabolism.^{98,166-172}

Although currently prescribed INSs demonstrate favorable degrees of first-pass hepatic inactivation compared with steroids prescribed for oral use, important differences exist among INSs.⁹⁸ For example, the percent of drug systemically available after oral administration has been estimated to be <1% for fluticasone propionate,¹⁷² <1% for mometasone furoate,¹⁶⁶ 10.6% for triamcinolone acetonide, 11% for budesonide,¹⁶⁷ 21% for flunisolide,¹⁶⁸ and 41% for beclomethasone dipropionate.¹⁶⁹ Absorption of drug across (ie, not merely into) the nasal mucosa into the circulation also varies significantly and is increased for agents with enhanced water solubility (eg, budesonide¹⁶⁵) compared with more lipophilic compounds (eg, mometasone furoate¹⁷⁰ and fluticasone propionate¹⁷¹). Consequently, estimated absolute bioavailability of a dose after intranasal administration varies from 49% (flunisolide)¹⁶⁸ to 44% (beclomethasone dipropionate)¹⁶⁹ to 34% (budesonide) to <1% (fluticasone propionate¹⁷¹ and mometasone furoate¹⁷⁰). Although differences exist between drugs in absorption across the nasal mucosa, clinically relevant differences in systemic bioavailability appear to reflect primarily the differences in oral bioavailability caused by different degrees of first-pass hepatic metabolism. Other important drug attributes (potency and lipophilicity) primarily affect therapeutic microgram-for-microgram comparisons but are less useful than oral bioavailability (that is, amount of drug that appears in circulation without first providing a therapeutic effect on the target organ) in predicting differences in the ratio between therapeutic and systemic effects between drugs.

The focus of this section is the interpretation of published studies as they relate to normal physiology of endocrine systems, methods of testing the function of these systems, and the known adverse effects of prolonged glucocorticoid excess. Understanding these complexities is critical to making the distinction between detectable indicators of systemic drug presence and a likely unwanted systemic effect.

INSs and the hypothalamic-pituitary-adrenal axis. The presence of any exogenous glucocorticoid in the bloodstream will reduce the need for endogenous cortisol production. Consequently, measurements of basal hypothalamic-pituitary-adrenal (HPA) activity, such as area under curve cortisol concentrations and urinary free cortisol excretion, provide the most sensitive indication of systemic bioavailability of INS, and these laboratory measures of HPA axis function are frequently used to compare systemic effects of INS. However, it is important to keep in mind that the mere presence of an exogenous glucocorticoid in circulation does not necessarily indicate risk of adverse consequences. Such effects are anticipated only if the exogenous glucocorticoid either exceeds normal cortisol production or provides a pattern of glucocorticoid exposure, which, by differing significantly

from normal diurnal fluctuations in cortisol levels, adversely affects other physiologic systems.

Tests of HPA axis function that assess basal cortisol production indicate that absorption of INS can occur in sufficient amounts to replace, to varying degrees, the need for endogenous cortisol production. For example, budesonide and beclomethasone dipropionate administered intranasally to healthy volunteers once in the evening or twice daily at doses of 200, 400, or 800 $\mu\text{g}/\text{d}$ have been reported to suppress urinary free cortisol excretion to varying degrees.¹⁷³ However, although these results can be considered biological markers of systemic glucocorticoid activity, they do not indicate clinical adrenal dysfunction.

Stimulation tests of the HPA axis are less sensitive in detecting the presence of systemically bioavailable INS but are more predictive of a possible clinically significant effect. Given the small apparent effects of INS on basal HPA axis function, abnormal responses to adrenal axis stimulation tests would not be expected. Studies using dynamic tests of adrenal function (eg, standard-dose ACTH stimulation test) have shown no significant effects of INS alone in adults with rhinitis (beclomethasone dipropionate 336 $\mu\text{g}/\text{d}$,¹⁷⁴ fluticasone propionate 200 μg once daily or 400 μg twice daily,¹⁷⁵ and triamcinolone acetonide 220 or 440 $\mu\text{g}/\text{d}$ ¹⁷⁶). In children, intranasal administration of triamcinolone acetonide 220 and 440 $\mu\text{g}/\text{d}$ for 6 weeks did not result in suppression of response to standard-dose ACTH.¹⁷⁷ Recent longer-term (1-year) studies of prepubertal children treated with either beclomethasone dipropionate 168 μg twice daily¹⁷⁸ or mometasone furoate 100 μg once daily¹⁷⁹ also showed no effects on ACTH responsiveness. Although these studies are reassuring, it is now known that low-dose (eg, 0.5- μg) ACTH stimulation testing may more accurately detect adrenal gland suppression than the standard-dose (250- μg) test.¹⁸⁰ When low-dose ACTH stimulation was used in healthy volunteers to assess HPA axis function after very short-term treatment with intranasal fluticasone propionate 200 $\mu\text{g}/\text{d}$, intranasal-triamcinolone acetonide 220 $\mu\text{g}/\text{d}$, or intranasal beclomethasone dipropionate 336 $\mu\text{g}/\text{d}$, no significant suppression was observed.¹⁸¹ Confirmation of normal responses to low-dose ACTH stimulation after more prolonged treatment with INS should be a future objective.

In addition to being affected by the choice of tests used, results of HPA axis studies are profoundly influenced by frequency of drug administration. Cortisol levels normally decrease steadily and fairly rapidly after the early morning peak, and daytime/evening production of cortisol is significantly reduced compared with nocturnal/early morning production. Consequently, morning administration of INS would be expected to have relatively little effect on (already declining) daytime cortisol concentrations. In addition, because both endogenous cortisol and systemically absorbed INS levels would be low in the evening after morning administration, there would be minimal disruption of the normal diurnal HPA axis rhythm. Studies examining once-daily (ie, morning)

administration of INS (beclomethasone dipropionate 336 $\mu\text{g}/\text{d}$,¹⁸¹ triamcinolone acetonide 220 $\mu\text{g}/\text{d}$,^{181,182} mometasone furoate 200 $\mu\text{g}/\text{d}$,¹⁸² budesonide 200 $\mu\text{g}/\text{d}$,¹⁸² and fluticasone propionate 200 $\mu\text{g}/\text{d}$, when urine collections were corrected for creatinine)^{181,183,184} show no significant effect on basal HPA axis function.

Interpreting studies on INS effects on the HPA axis is also made more difficult for readers by microgram-for-microgram comparisons, which ignore known differences in drug potency. Marked differences in receptor affinity between, for example, intranasal fluticasone propionate or mometasone furoate and intranasal triamcinolone acetonide should obviate a direct comparison of similar-microgram doses, as it would a milligram-for-milligram comparison between oral hydrocortisone and prednisone. More informative would be comparisons of clinically equivalent doses of compounds. In addition, subtle decisions regarding data description can affect conclusions drawn. For example, one report concluding that overnight urinary cortisol was significantly suppressed by intranasal fluticasone propionate 200 $\mu\text{g}/\text{d}$ ¹⁸¹ was contradicted when collections were corrected for creatinine excretion.^{183,184}

Taken together, the data suggest that administration of INS alone in recommended and moderate doses has minimal effects on the HPA axis. Substantial differences in the attributes of individual INS, such as oral bioavailability, may affect studies of basal HPA axis function, particularly after nocturnal administration, but have not been shown to have clinical relevance with regard to adrenal gland responsiveness. Once-daily administration of recommended doses of INS appears to have negligible effects on the HPA axis and, from a safety standpoint, should be preferred if effective and particularly if higher INS dosage is required. Additive exogenous steroid effects on the HPA axis, however, can occur when INS treatment accompanies concurrent ICS or other topical corticosteroid therapy.

INSs and childhood growth. Corticosteroids are potent inhibitors of linear growth, exerting suppressive effects at virtually every level of a child's growth axis.¹⁸⁵ Blunting of pulsatile growth hormone release, downregulation of growth hormone receptor expression, inhibition of insulin-like growth factor 1 bioactivity, and suppression of collagen synthesis and adrenal androgen production are all known mechanisms by which corticosteroids can inhibit growth. Small amounts of exogenous corticosteroid in excess of normal physiologic requirements are capable of suppressing childhood growth.¹⁸⁶ Consequently, growth suppression is both a sensitive and relatively specific indicator of excessive corticosteroid effect, which distinguishes it from highly sensitive measures of basal HPA axis function that have limited predictive value for clinically meaningful effects.

In addition to drug properties that influence the degree of systemic effects observed at a given dosage, patient characteristics also affect susceptibility to growth suppression. These include age and growth pattern of the child, underlying disease severity, and timing of drug

administration. Childhood growth can be conceptually divided into age-related phases: (1) a rapid but rapidly decelerating period during infancy controlled primarily by nutrition and nutrition-dependent growth factors; (2) childhood growth, during which growth rate, under primary regulation by growth hormone, gradually declines; (3) and pubertal growth, during which growth rate accelerates under combined growth hormone and sex hormone stimulation, then declines as epiphyseal closure occurs.^{187,188} In some children, susceptibility to growth suppression by a variety of influences is increased during transitions from one phase to another. This is particularly true in the 2 to 3 years before puberty, when growth rates are low and the resiliency of the growth hormone axis is transiently, physiologically low. Significantly, most studies of growth effects of INS or ICS have focused on children of this age, and results cannot confidently be extrapolated to infants or adolescents.

Chronic disease during childhood is known to affect adversely the tempo of growth, an effect observed in children with asthma predominantly late in childhood and early in adolescence.¹⁸⁹ Pubertal development and attainment of (normal) adult height is delayed. In contrast with asthma, however, allergic rhinitis alone does not appear to have an important effect on growth. Timing of drug administration, on the other hand, may be important. Growth hormone secretion in prepubertal children is pulsatile and primarily nocturnal, with initiation of pulses corresponding to the normal late-evening nadir in plasma cortisol concentrations. Absorption of exogenous corticosteroid at that time might be expected to have a more pronounced suppressive effect on growth hormone release than morning dosage. Consistent with this, short-term studies of intranasal budesonide suggest that 200 μg twice daily causes significant suppression in short-term lower-leg growth,¹⁹⁰ whereas 400 μg administered once daily in the morning does not.¹⁹¹

Recent observations that certain ICSs can measurably slow growth rates in prepubertal children with asthma^{192,193} prompted concerns about a possible similar effect from chronic INS. Studies using stadiometry have revealed detectable differences in the effects of various INS and/or dosing regimens on growth.^{178,179} A 12-month, double-blind, placebo-controlled study of prepubertal children with perennial allergic rhinitis demonstrated that intranasal beclomethasone dipropionate 200 μg (delivered dose, 168 μg) twice daily caused a small (0.9-cm) but statistically significant reduction in annual height gain (Fig 9).¹⁷⁸ Subtle problems with study design (eg, older average age of beclomethasone-treated children) may have exaggerated the observed growth effect, but correcting the results for differences in expected growth rates did not eliminate a significant drug effect.

In contrast with intranasal beclomethasone, 1-year treatment using intranasal mometasone furoate 100 μg once daily showed no evidence of growth retardation (Fig 10).¹⁷⁹ Neither has intranasal fluticasone propionate alone been found to have any effect on growth in prepubertal children over a year of observation. Consistent with this,

one study examining the addition of INS to ICS treatment for asthma (inhaled beclomethasone dipropionate 200 μg twice daily or inhaled fluticasone propionate 100 μg twice daily) found no effect on 1-year growth when intranasal fluticasone propionate was added to either inhaled fluticasone propionate or inhaled beclomethasone dipropionate therapy, whereas the addition of intranasal beclomethasone dipropionate resulted in growth suppression of both inhaled fluticasone propionate-treated and inhaled beclomethasone dipropionate-treated children.¹⁹⁴ Furthermore, data extrapolated from a study of the long-term growth effects of inhaled fluticasone propionate, which is associated with a higher bioavailability (26.4%) than intranasal administration (<1%¹⁷¹), would predict no significant effect of a similar dose of intranasal fluticasone propionate. In this prospective and tightly controlled 12-month study of prepubertal children with asthma, administration of inhaled fluticasone propionate 50 μg or 100 μg twice daily had no significant effect on growth.¹⁹⁵ A long-term evaluation of the effect of intranasal budesonide in children with asthma has determined that such children attain normal adult height.¹⁹⁶

These studies allow the following conclusions to be drawn regarding the effects of INS given in therapeutic doses on childhood growth: (1) detectable slowing of 1-year growth in prepubertal children can occur with continuous, twice-daily treatment with intranasal beclomethasone dipropionate; (2) long-term effects of intranasal beclomethasone dipropionate on growth or adult height remain unknown; (3) once-daily administration of recommended doses of an INS with more efficient first-pass hepatic inactivation (eg, fluticasone propionate or mometasone furoate) should not suppress growth; (4) twice-daily administration of an INS may be required to cause detectable growth suppression; (5) because total systemic corticosteroid burden reflects absorption of exogenous corticosteroid administered by any route, the risk for growth suppression is increased when INS and ICS therapies are combined; and (6) titration to the lowest effective dose, a once-daily dosing regimen, and the choice of an INS with efficient inactivation of swallowed drug will minimize the already low risk of growth suppression by INS therapy alone.

INSs and effect on bone metabolism and risk for osteoporosis. Corticosteroid excess affects normal bone metabolism in multiple ways: calcium homeostasis is disrupted by direct alteration of osteoblastic and osteoclastic activity leading to increased bone dissolution.¹⁸² Increases in urinary calcium losses coupled with inhibition of vitamin D-mediated intestinal calcium absorption result in total body calcium deficiency and secondary hyperparathyroidism.¹⁹⁷ In women in particular, reductions in sex hormone production further reduce bone mass. Thus, an important long-term side effect of corticosteroid excess is osteoporosis and the associated increased risk of fractures.

Although the adverse effects of corticosteroids on bone metabolism are well known, determining possible effects of INS or ICS on this system is challenging. Multiple

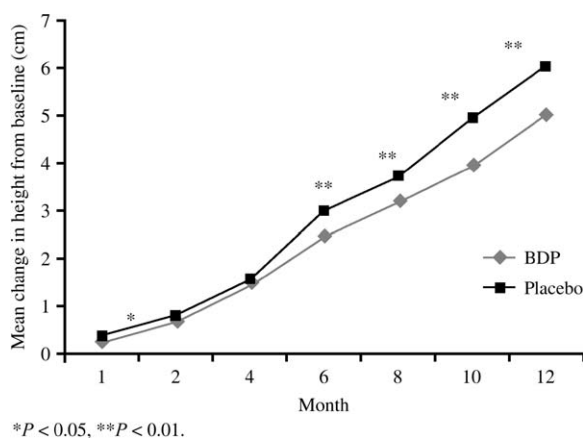


FIG 9. Change in height over 1 year in children treated with beclomethasone dipropionate 200 µg twice daily or placebo showing a significant reduction in growth in those receiving the intranasal steroid. Asterisks indicate time-points of significant difference between active and placebo therapy. BDP, beclomethasone dipropionate. Reproduced with permission from *Pediatrics*, Vol 105(2), page E23. © 2000 by the AAP.¹⁷⁸

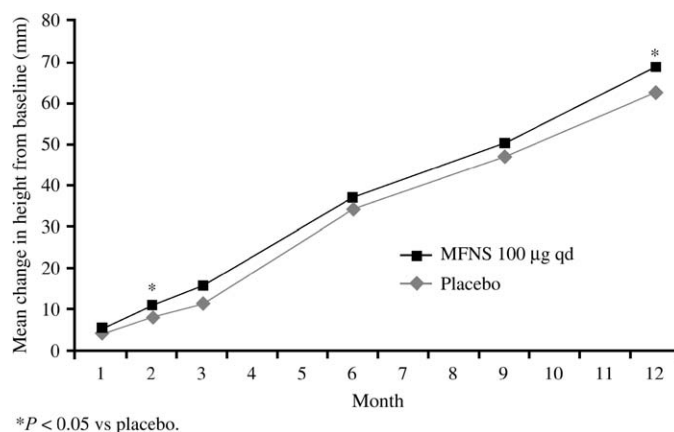


FIG 10. Change in height over 1 year in children treated with intranasal mometasone or placebo showing no deleterious effect of this intranasal steroid on growth. * $P < 0.05$ for increased growth in mometasone-treated children. MFNS, mometasone furoate nasal spray. Reproduced with permission from *Pediatrics*, Vol 105(2), page E22. © 2000 by the AAP.¹⁷⁹

potentially confounding factors must be considered, such as nutrition history, heredity, the control of underlying disease, the extent of physical activity, and previous exposure to oral corticosteroids. In children, the stage of development is also critical, because the rate of bone mineral accretion increases rapidly in adolescence, and delayed puberty itself is associated with significantly lower peak bone mass/density.¹⁹⁸ Short-term effects of exogenous steroids on bone can be evaluated by measuring biochemical markers of bone formation (eg, osteocalcin) and degradation (eg, urinary telopeptides). However, the predictive value of changes in markers of bone turnover for clinically important adverse effects is unproven. Dual x-ray absorptiometry is the most valid technique for assessing bone mineral density (BMD). However, even the finding of reduced BMD has only a statistical association with future fracture risk and is of marginal clinical utility for assessing risk in individual patients; that

is, a decrease of 1 population SD in BMD is associated with a doubling of the risk of fracture from data in older women.¹⁹⁹

Although studies investigating the association between ICS treatment and BMD in adults have given inconsistent results, recent data provide evidence for a negative relation between total cumulative ICS dose (~80% of patients using inhaled beclomethasone dipropionate) and BMD in patients with asthma.²⁰⁰ As indicated, the importance of this observation to the effects of ICS and INS treatment in individual patients rather than to expected effects of INS alone on BMD. Presently, there are limited data examining the long-term effects of INS on BMD. No studies using dual x-ray absorptiometry measurements of INS-treated children or adults could be found. Short-term intranasal administration of budesonide 200 µg/d, triamcinolone acetonide 220 µg/d, or mometasone furoate

200 µg/d resulted in no suppression of plasma osteocalcin levels.¹⁸² Nevertheless, studies of HPA axis function and growth during INS therapy allow predictions to be made for bone metabolism, because these systems offer more sensitive indicators of systemic corticosteroid effect. Therefore, INS treatment regimens that do not suppress basal measures of HPA axis function and have no detectable effects on childhood growth would be expected to have no significant effect on osteoporosis risk. As mentioned, when INSs are used in combination with corticosteroids administered by other routes, small increases in systemic corticosteroid effect resulting from INS use could theoretically occur, and the choice of an INS with minimal oral bioavailability would be advised.

SUMMARY

Allergic rhinitis is recognized by the classical anterior nasal symptoms of itch, sneeze, discharge, and obstruction. Although these are usually assessed on symptomatic rating scales in clinical trials, it is appreciated that the nasal mucosa is not the only mucosal surface affected as part of the allergic disease and that there are systemic manifestations of the allergic inflammation at these sites and a range of associated features that affect the well-being of the individual. The sole recording of nasal symptoms in allergic rhinitis does not thus evaluate the full effect of the disease, and specific measures to assess QOL have been developed. Both seasonal and perennial rhinitis may cause quite severe impairment of HRQL. There is a poor correlation between clinical indices of nasal inflammation and HRQL, and therefore, HRQL must be measured directly and cannot be imputed from the clinical indices. There are valid, disease-specific instruments available for measuring HRQL in both adults and children with rhinitis, enabling this outcome measure to be included in both clinical trials and clinical practice. The use of HRQL measures helps focus on those components of rhinitis that are most important to the patient.

Health-related QOL is not only influenced by the disease itself but also potentially affected by the administered therapy. The loss of sense of smell in more severe disease additionally affects QOL and can be tested for by validated tests such as UPSIT and STT methods. Ubiquitous and underrecognized CNS toxicity from first-generation H₁-antihistamines, which is easy to measure objectively, contrasts with rare cardiac toxicity from second-generation H₁-antihistamines, which is also easy to measure objectively. Both kinds of H₁-antihistamine toxicity are completely avoidable if physicians recommend only H₁-antagonists with an excellent safety profile. Monitoring for these effects is essential in trials of new antihistamines.

Although topical airway corticosteroid therapies for asthma and allergic rhinitis have markedly improved the control of these diseases while significantly lessening the

risk of corticosteroid side effects, the use of these therapies continues to be accompanied by public fear of potential adverse systemic effects. Unfortunately, these fears result in some patients being deprived of appropriate and effective treatment, or even exposed to a greater risk of periodic oral corticosteroid treatment. Nevertheless, continued development of more potent INS compounds, which will be increasingly used for longer periods in patients with mild disease and in younger patients, demands careful examination of potential systemic effects.

Although INSs have not been nearly as thoroughly investigated as ICSs, information is now rapidly accumulating to support the safety of INSs used in recommended doses. Some important overall conclusions appear both to be well supported by the studies taken together and to make sense from an endocrinologic point of view. First, although potentially detectable in the systemic circulation after administration, INSs used in small doses or intermittently present no significant risk for systemic side effects. When INSs are used at higher dosages and continuously for long periods, important differences in drug characteristics, particularly the efficiency of inactivation of swallowed drug (which does not exert a therapeutic effect before gaining access to the systemic circulation), affect the ratio of therapeutic to systemic effect of individual INSs. Once-daily morning INS administration, which prevents a nonphysiologic corticosteroid effect during the normal late evening nadir in endogenous cortisol levels and increase in growth hormone secretion, reduces any potential suppression of the HPA or growth axis.

From a practical viewpoint, the long-term clinical history of INS therapy is informative. Clinically significant suppression of the HPA axis as a result of standard-dose INS therapy alone appears to be exceptionally rare. Detectable suppression of childhood growth was observed when an INS with relatively poor first-pass inactivation was administered twice daily continuously throughout the year. Once-daily administration of INS has not been associated with a clinically relevant effect on either HPA axis function or childhood growth. Harmful effects of INS on bone metabolism, although not yet adequately studied, would not be expected with the use of an INS, dose, and dosing frequency that do not suppress basal HPA axis function or childhood growth. An important caveat to these conclusions is that they refer to the use of INSs alone, not when used in combination with ICSs or other topical corticosteroids, when the total delivery has to be assessed. The incorporation of measures of systemic potential, such as effects on HPA axis and growth, are important endpoints in any long-term study of INSs in children.

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