

REVIEW

Identification and management of undiagnosed and undertreated allergic rhinitis in adults and children

M. G. Stewart

Department of Otorhinolaryngology, Weill Medical College of Cornell University, New York, NY, USA

Clinical and Experimental Allergy

Summary

Allergic rhinitis (AR) is a common health problem that affects adults, adolescents and children and is often undiagnosed or inadequately treated. Because AR is not a life-threatening disease, many patients do not seek medical treatment for their symptoms, and others self-medicate with over-the-counter medications, often sedating antihistamines. However, untreated or inadequately treated AR can substantially impair overall quality of life (QOL) by causing fatigue, headache, cognitive impairment and other problems. The risk for comorbid conditions, such as asthma, otitis media, and lymphoid hypertrophy with obstructive sleep apnea, can increase, and the symptoms of AR can worsen if AR is not adequately treated. Among the symptoms of AR, nasal congestion has been described by patients as the most bothersome because it disrupts sleep, resulting in diminished daytime performance. A new congestion screening tool, the Congestion Quantifier, has been developed to aid in the diagnosis and treatment of AR and to help guide treatment decisions. Intranasal corticosteroids (INSs) are recommended as effective pharmaceutical treatments for controlling the symptoms of AR. Randomized, controlled trials in children and adults have demonstrated that INSs relieve rhinitis symptoms, thereby improving QOL in individuals with seasonal or perennial AR. Most INSs are approved for use in children ≥ 6 years of age, but mometasone furoate and fluticasone furoate are approved for use in children as young as 2 years of age and fluticasone propionate for children ≥ 4 years old. Long-term benefits have also been seen with the use of immunotherapy, although some patients, especially children, resist the injections used in subcutaneous immunotherapy. Recent studies with sublingual immunotherapy have indicated that it might be an effective and well-tolerated alternative to immunotherapy injections.

Correspondence:

Michael G. Stewart, Department of Otorhinolaryngology, Weill Medical College of Cornell University, 1305 York Ave, 5th Floor, New York, NY 10021, USA.
E-mail: mgs2002@med.cornell.edu

Introduction

Allergic rhinitis (AR) is a very common disease, affecting 10–25% of the population world-wide [1–3]. In the United States, AR was the fifth most prevalent chronic health condition in the 1990s, occurring in 10–30% of adults and up to 40% of children [4–7]. Seasonal AR, which had an estimated prevalence of as much as 40% of the US population, accounts for most cases of AR and is more prevalent in children and adolescents [1]. In comparison, during the same time period, Europe appeared to have a lower prevalence of seasonal AR, ranging from 3% in the United Kingdom up to 22.7% in Germany. Perennial AR has a world-wide prevalence ranging from 1% in Switzerland to 5% in the United States and to 13% in the United Kingdom [1]. The prevalence of both types of AR has increased over the past 40 years, possibly as a result of

changes in lifestyle and increased exposure to allergens and airborne pollutants and/or irritants [1].

The actual number of individuals affected by AR may be underestimated, because many are undiagnosed or do not seek treatment from a physician. Surveys in Europe and the United States concluded that AR was undiagnosed in about one-third of adults with the condition, and that only about 12% of people with AR sought prescription treatment [8, 9]. The consequences of undiagnosed or inadequately treated/untreated AR extend to an increased risk for comorbid conditions (e.g. asthma, rhinosinusitis, and otitis media), exacerbation of AR symptoms, impaired quality of life (QOL), and diminished performance at work or school [9–14].

This review discusses the extent to which AR is undiagnosed and untreated, or inadequately treated, and how this, in turn, impacts health and QOL in both adults

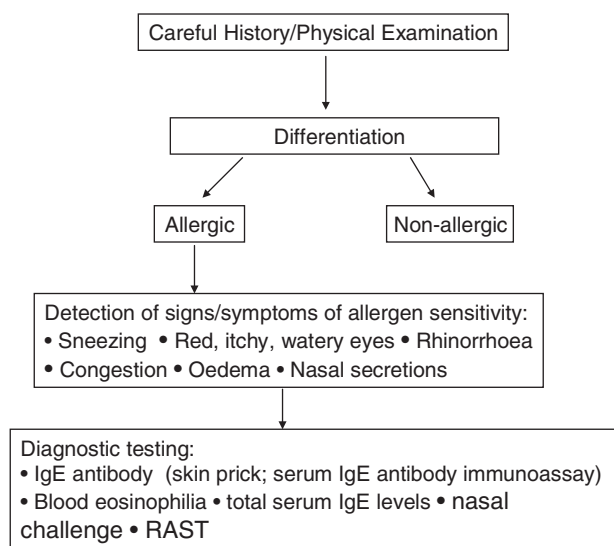


Fig. 1. Diagnosis of allergic rhinitis.

and children. Intranasal corticosteroids (INs) have been shown to be effective for all of the nasal symptoms of AR and are recommended for their treatment [15]. The results of representative studies demonstrating the efficacy of the INs currently approved for use in the United States (i.e. beclomethasone dipropionate, budesonide, flunisolide, triamcinolone acetonide, fluticasone propionate, mometasone furoate, and fluticasone furoate) in adults and children with seasonal AR and in adults with perennial AR are summarized.

Diagnosis

The effective treatment of AR begins with an accurate diagnosis, which ideally will consider multiple factors (Fig. 1). Although helpful, positive tests for allergen-specific IgE are not sufficient for a positive diagnosis of AR. Rather, physicians should review the clinical history of a patient to differentiate allergic from non-allergic rhinitis and to identify the specific allergens involved. Ultimately, diagnosing AR involves looking at a constellation of parameters, including positive family history, the presence of comorbidities, and whether the symptoms observed result from IgE-mediated inflammation [16].

Consequences of undiagnosed or inadequately treated/untreated allergic rhinitis

Although the consequences of undiagnosed or inadequately treated AR are well known, epidemiological studies and patient surveys have concluded that poor diagnosis and undertreatment remain a persistent problem. A survey of a random sample of Danish adolescents and adults ($N=1149$) found that AR was previously undiagnosed in 32% who reported or were treated for

symptoms, and that 83% of those with moderate-to-severe AR were untreated [8]. AR is often undiagnosed in children, who typically are unable to articulate their symptoms [17, 18]. Unlike adults, children rarely complain about specific symptoms of AR. Instead, they commonly present with recurrent sore throats and upper respiratory tract infections. The diagnosis of AR is therefore often missed and the child is treated inappropriately with antibiotics [13]. Data from 1402 questionnaires of the International Study of Asthma and Allergies in Childhood revealed that although 16.8% of pre-schoolchildren had non-cold-related nasal symptoms over a 12-month period, only 4% were diagnosed with AR by a physician [19].

When AR is undiagnosed, inadequately treated, or untreated, symptoms (nasal congestion, rhinorrhea, sneezing, and nasal itching) can have a substantial impact on the individual's QOL [20–28] (Table 1). Untreated symptoms can lead to fatigue, headache, cognitive impairment or inability to concentrate, and other problems [5, 13, 21–23]. Children with chronic AR typically have hypernasal speech, fatigue, decreased appetite, and growth retardation [11, 13]. Children with severe AR often have facial manifestations of itching, mucosal oedema of the nose and sinuses, and obstructed breathing [25, 26].

Comorbidities

Undiagnosed or poorly treated/untreated AR is also associated with comorbid conditions, including asthma, acute maxillary rhinosinusitis, otitis media with effusion or chronic middle ear effusions, and lymphoid hypertrophy with obstructive sleep apnea (OSA), as well as disordered sleep with consequent behavioural and learning problems and diminished performance or productivity at work and/or school [1, 6, 13, 22, 24, 28–31]. For example, 60–78% of patients with asthma have coexisting AR, and from 19% to 59% of patients with AR experience asthma [8, 32, 33]. AR has also been implicated as a factor contributing to acute maxillary rhinosinusitis in approximately 25–30% of patients compared with 16.5–19.5% of controls [30].

Nasal inflammation from AR can contribute to otitis media and otitis media with effusion [34]. Epidemiologic data indicate that 40–50% of children over 3 years of age with chronic otitis media have documented AR, and that patients with AR, particularly children, have a higher risk of eustachian tube dysfunction [31, 34, 35]. A study of middle ear effusions and adenoidal tissue biopsies from 45 patients aged 2–18 years undergoing simultaneous tympanostomy tube placement for otitis media with effusion and adenoidectomy for adenoid hypertrophy found that in the 24% who were atopic, allergic inflammation occurred on both sides of the eustachian tube, supporting the concept that the middle ear is part of the unified airway in atopic individuals [36]. However, a connection

Table 1. Impact of untreated symptoms of allergic rhinitis on health and quality of life

General Population
<i>Physical complaints:</i> headache, fatigue (disrupted sleep), impaired physical functioning [5, 20, 21]
<i>Cognitive impairment:</i> reduced ability to concentrate, decreased verbal learning, slower decision-making and psychomotor speed, slower cognitive processing, difficulties with working memory [21–23]
<i>Emotional functioning:</i> lower positive affect, emotional distress [20, 22]
<i>Workplace performance:</i> absenteeism, loss of productivity [9, 14, 24]
Children [11, 13, 25–28]
<i>General physical findings:</i> hypernasal speech, fatigue, decreased appetite, poor growth
<i>Facial manifestations of mucosal oedema and itching:</i> allergic shiner, salute or crease
<i>Facial manifestations of obstructed breathing:</i> gaping mouth, chapped lips, elongated face, dental malocclusions
<i>Educational problems:</i> learning impairment, frequent school absences, poorer performance in school, difficulty in concentrating

between AR and otitis media is not accepted by all authorities [1].

Adenotonsillar hypertrophy is frequently present in children with AR [13, 37]. A study of 28 children with seasonal AR and documented hypersensitivity to birch tree pollen found a significant increase in adenoid size in 71% and a decrease in nasopharyngeal cavity volume in 93% during the pollen season [38]. These changes disappeared in 90% of the children after the pollen season. In young children, nocturnal snoring and OSA are associated with adenotonsillar hypertrophy and chronic rhinitis, and in children with habitual snoring, the presence of allergy increases the risk of OSA [39]. Among 39 children with habitual snoring who were referred to a sleep disorders clinic, 14 (36%) had a positive multi-antigen radioallergen sorbent test (RAST): higher than expected for the general population [39]. The frequency of OSA was 57% in those with positive RAST results compared with 40% in those with negative RAST results ($P < 0.01$) [39].

Nasal congestion

AR frequently causes nasal congestion, which is thought to contribute to sleep-disordered breathing (SDB). In a population-based sample, participants who experienced night-time symptoms of AR for five or more nights a month were significantly ($P < 0.0001$) more likely to report habitual snoring, chronic excessive daytime sleepiness, or chronic non-restorative sleep than those who rarely or never had symptoms [40]. Participants who reported nasal congestion due to allergy were 1.8 times more likely to have moderate-to-severe SDB than those without nasal congestion due to allergy [40].

Nasal congestion appears to be the symptom associated with the most severe consequences for individuals in whom AR is inadequately treated or untreated. Recent surveys of AR sufferers in the United States and Europe identified nasal congestion as the predominant symptom reported by respondents [41, 42]. An internet survey of individuals with AR or those who were primary caregivers of a child with AR, which was conducted in the United

States from May to June 2004, found that nasal congestion was the symptom that 50% of adults and 63% of children most wanted to prevent, and the one that was most likely to prompt a visit to a physician [41] (Table 2). Nasal congestion affected 80% or more of respondents in some way at night, causing them to wake up or making it difficult to fall asleep [41]. The effect of nasal congestion on sleep increased as the severity of congestion intensified – from 71% in respondents with mild congestion, to 83% in those with moderate congestion, to 90% in those with severe congestion [41]. Of 1034 adult respondents who were employed, 59% reported that nasal congestion impaired their job performance, 42% were not able to concentrate, and 36% reported poor productivity [41].

A survey of patients from five countries (France, Germany, Italy, Spain, and the United Kingdom) in July and August 2005 sought to establish the nature of allergy symptoms, the prevalence of congestion, and the impact of congestion on sleep [42]. At least 49% of 3036 respondents reported nasal and/or sinus congestion of any severity, and the majority of those reporting congestion said that it made breathing normally difficult. Congestion also had an adverse effect on the quality and quantity of sleep, and on the respondents' ability to function normally the next day (Fig. 2).

A brief, recently validated screening tool can be used to identify individuals with nasal congestion and help

Table 2. Respondents' ratings of self-reported nasal congestion ($N = 2002$) [41]

	Adults (%)	Children (%) [*]
Most bothersome AR symptom	48	58
Symptom most wanted to prevent	50	63
Symptom most likely to trigger a physician visit	54	69
Symptom affects sleep by		
Causing night-time awakening	51	49
Making it difficult to fall asleep	48	49

^{*}Rated by primary caregiver.

AR, allergic rhinitis.

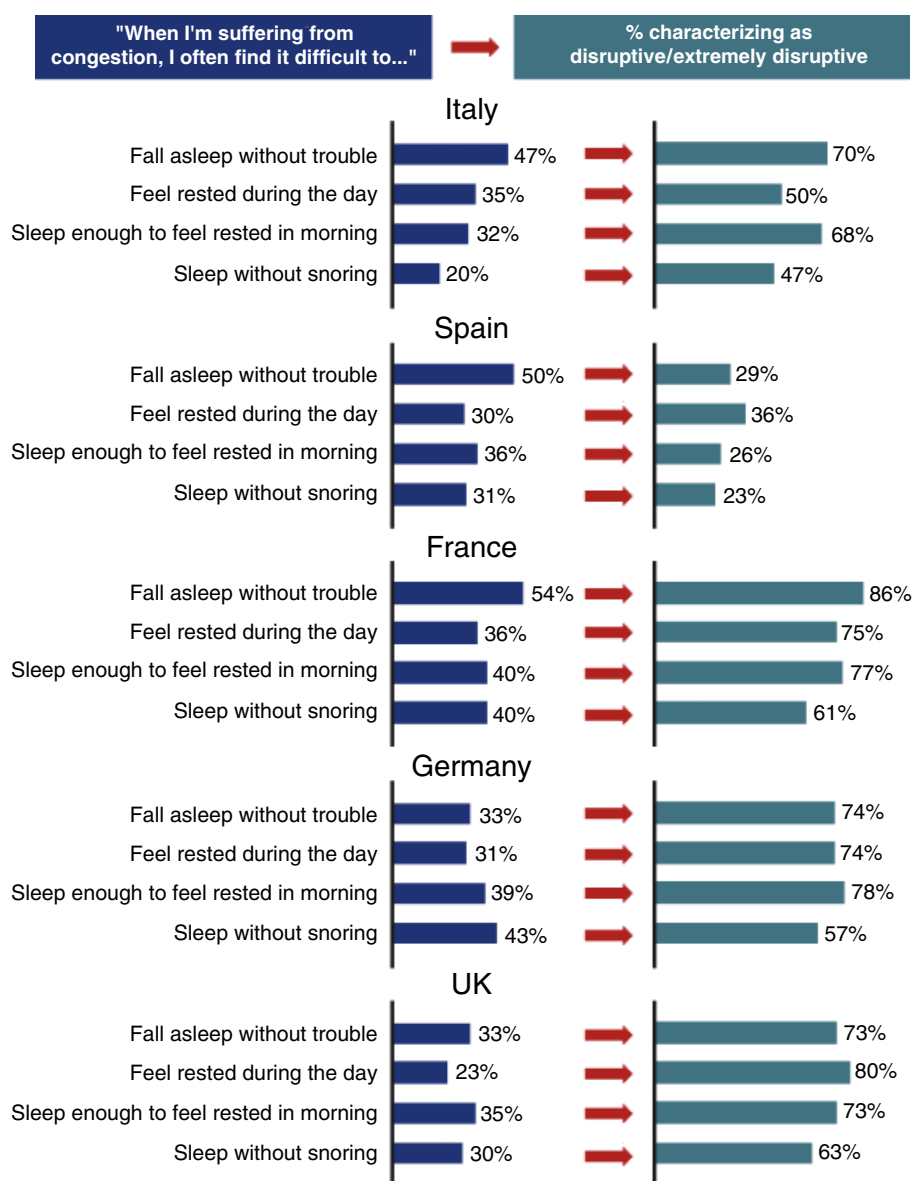


Fig. 2. Negative impact of nasal congestion on sleep by country [42].

patients determine if they should seek medical treatment [43]. The Congestion Quantifier was initially developed to have 13 questions about the impact of stuffiness/congestion on patients' lives. The seven categories quantifying the most deleterious effects of congestion, including headache/sinus pressure, rhinorrhea, and impairment of work and sleep, are included in the seven-item subset of the Congestion Quantifier – the CQ7 (Table 3). The CQ7 allows patients to quantify the occurrence of these effects during the past week using a scale of zero (none of the time) to four (all of the time) [43]. This screener can be completed by patients and used by patients and physicians together to identify treatable congestion symptoms.

Poor or disrupted sleep associated with AR causes behavioural and learning problems in children and

diminished performance and loss of productivity in adults (Table 1). Frequent AR-related absences from school lead to poor academic performance among children [9, 28, 29]. In addition, frequent sneezing and nose blowing by the child during the allergy season may disrupt the classroom and annoy classmates [29]. Children with AR may feel isolated, making them frustrated, sad, and angry [44]. Among adults, employees with allergies who report using no medication show a 10% decrease in productivity compared with workers without allergies [24]. A survey of more than 8000 US employees at 47 locations found that 55% experienced AR symptoms for an average of 52.5 days, were absent 3.6 days per year as a result of the condition, and were unproductive 2.3 h per workday when experiencing symptoms [14]. When AR is inadequately

Table 3. Seven-Item Congestion Quantifier

During the past week, how often did you	None of the time	A little of the time	Some of the time	Most of the time	All of the time
■ Have nasal stuffiness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
■ Have sinus pressure in your face?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
■ Have to breathe through your mouth because you couldn't breathe through your nose?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
■ Have difficulty completely clearing your nose, even after repeated blowing?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
■ Have any of these symptoms affect your work, learning in school, or other things you needed to do?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
■ Awaken in the morning with nasal stuffiness, blockage, or congestion?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
■ Have your sleep affected by nasal stuffiness, blockage, or congestion?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

treated or untreated, the costs of treating comorbid conditions increase substantially [45]. Indeed, medical costs for patients with asthma and AR are 46% higher than for those with asthma only [46].

Available treatments for allergic rhinitis

Separate surveys in the United States of individuals with self-reported AR found that 82% were taking a prescription or over-the-counter (OTC) medication for allergy symptoms [6, 41]. A survey of 2355 individuals with AR conducted in 2004 found that 81% ($n = 1925$) were taking medication to treat their allergies, of whom 60% (1146) were receiving a prescription medicine [41]. Only 13% of those taking any type of allergy medication were 'very satisfied' with their treatment, and those who were dissatisfied with a prescription medication were twice as likely to report that symptoms, especially nasal congestion, recurred most of the time after they took the medication [41]. Although INSs have been recommended as first-line treatment for this condition since 2001 in the guidelines issued by the Allergic Rhinitis and its Impact on Asthma Workshop Group, only 25% of respondents in the 2004 survey were taking an INS either alone or in combination with another prescription or OTC medication [1, 41, 47]. In addition, only 30% of survey respondents with severe congestion were using INSs – the agents recommended for this condition [1, 41].

Many individuals with AR self-medicate with OTC products, and 47–52% use OTC antihistamines [48]. In one survey, nearly 60% of those self-treating AR were using an OTC sedating antihistamine, which have been associated with diminished performance at work or school, and a significantly increased risk of work-related and other accidents [5, 6, 49–53]. Using a health claims database, a retrospective cohort study compared rates of injury in 12 106 patients initially prescribed diphenhydramine and 24 968 patients initially prescribed loratadine [53]. Injury rates in the 30 days before prescription were comparable in the diphenhydramine and loratadine groups (128 and 125 per 1000 person-years, respectively). However, during the 30 days after the initial prescription,

the injury rate increased to 308 per 1000 person-years in the diphenhydramine group compared with 137 per 1000 person-years in the loratadine group. An estimated 55% of the injuries in the diphenhydramine group were attributable to the drug [53].

Intranasal corticosteroids

The efficacy of INSs (i.e. beclomethasone dipropionate, budesonide, flunisolide, triamcinolone acetonide, fluticasone propionate, mometasone furoate, and fluticasone furoate) for the treatment of nasal symptoms of AR has been demonstrated in multiple randomized, double-blind, placebo-controlled trials in adults and children with seasonal AR and in adults with perennial AR [1]. The results of representative studies are summarized in Table 4 [54–62]. Overall, these studies show that INSs improve nasal symptoms (i.e. congestion, itching, rhinorrhea, sneezing) and relieve sinus pain and pressure. Evidence is also emerging that some INSs may relieve ocular symptoms (i.e. itching/burning, tearing, redness) as effectively as oral non-sedating antihistamines [62–64]. By reducing the symptoms of AR, INSs have also improved the QOL issues associated with the disorder [58–61, 65]. Overall, a vast body of clinical evidence demonstrates that INSs effectively relieve nasal symptoms in children and adults with seasonal and perennial AR, and that they are well tolerated, with the most common side-effects reported being headache and epistaxis.

Budesonide aqueous nasal spray. Double-blind, placebo-controlled trials conducted before 2000 have shown that intranasal budesonide effectively relieves symptoms of seasonal and perennial AR in adults and children [1]. More recently, the efficacy of budesonide aqueous nasal spray (128 mcg once daily) was evaluated in a double-blind, randomized, placebo-controlled, multi-country study in children ($N = 202$) aged 6–16 years with perennial AR [59]. Compared with placebo, budesonide was associated with statistically significant improvements in morning and evening combined nasal symptom scores (blocked nose+runny nose+sneezing) and peak nasal inspiratory

Table 4. Major single- and double-blind clinical trials demonstrating efficacy of intranasal corticosteroids in allergic rhinitis

Intranasal treatments	Reference	Patients (N)/Age/ Dx	Duration	Results
Mometasone furoate (MF) 200 mcg q.d. (<i>n</i> = 181) Fluticasone propionate (FP) 200 mcg q.d. (<i>n</i> = 183) Placebo (<i>n</i> = 184)	Mandl et al. [54]	<i>N</i> = 550, 12–77 years PAR	3 months	MF significantly more effective than placebo (<i>P</i> < 0.01) and comparable to FP in reducing total AM+PM daily nasal symptom score over the first 15 days of treatment
MF 200 mcg (<i>n</i> = 122) Placebo (<i>n</i> = 123)	Gawchik et al. [55]	<i>N</i> = 245, ≥ 12 years SAR	14 days	Significantly greater improvements in daytime (<i>P</i> < 0.01) and nighttime (<i>P</i> < 0.05) nasal congestion, and total daytime and night-time nasal symptoms with MFNS than placebo (<i>P</i> ≤ 0.017)
Triamcinolone acetonide (TAA) 220 mcg q.d. (<i>n</i> = 148) Fluticasone propionate (FP) 200 mcg q.d. (<i>n</i> = 147)	Berger et al. [56]	<i>N</i> = 295, 12–70 years spring SAR	3 weeks	Both treatments produced statistically significant reductions from baseline in total nasal symptom score and individual symptoms (<i>P</i> < 0.05), with no significant differences between treatments
TAA 220 mcg q.d. (<i>n</i> = 172) FP 200 mcg q.d. (<i>n</i> = 180)	Gross et al. [57]	<i>N</i> = 352, 12–70 years fall SAR	3 weeks	Improvements in daily total nasal symptom scores were similar: 49.4% with TAA and 52.7% with placebo. For individual nasal symptoms, the only significant difference between treatments was a greater reduction in sneezing at week 2 with FP (<i>P</i> = 0.046)
TAA 220 mcg q.d. (<i>n</i> = 75) Beclomethasone dipropionate (BDP) 336 mcg b.i.d. (<i>n</i> = 77) Budesonide (BUD) 128 mcg q.d. (<i>n</i> = 100) Placebo (<i>n</i> = 102)	Lumry et al. [58]	<i>N</i> = 152, ≥ 18 years SAR	3 weeks	Rhinoconjunctivitis Quality of Life (QOL) Questionnaire scores were similar for TAA and FP overall; for individual items FP produced a significantly greater improvement in emotions (<i>P</i> = 0.04) Both TAA and BDP were effective in relieving nasal and ocular symptoms, with no significant differences between treatments. Both agents were equally effective in improving health-related QOL
FP 200 mcg q.d. Loratadine 10 mg q.d. Placebo	Fokkens et al. [59]	<i>N</i> = 202, 6–16 years PAR	6 weeks	BUD significantly more effective than placebo in improving peak nasal inspiratory flow (<i>P</i> < 0.001), combined and individual nasal symptom scores (<i>P</i> < 0.01 to <i>P</i> < 0.001), and overall evaluation of treatment efficacy (<i>P</i> < 0.001). Paediatric and adolescent QOL scores (<i>n</i> = 76) were reduced, but the difference between BUD and placebo was not significant
FP 200 mcg q.d. (<i>n</i> = 101) Placebo (<i>n</i> = 105)	Bender et al. [60]	<i>N</i> = 60, 8–17 years SAR	22 days	FP significantly improved nasal symptom control (<i>P</i> = 0.03), nasal QOL score (<i>P</i> = 0.03), and verbal memory (<i>P</i> < 0.05)
Fluticasone furoate (FF) 110 mcg q.d. (<i>n</i> = 151) Placebo (<i>n</i> = 148)	Ratner et al. [61]	<i>N</i> = 206, ≥ 12 years SAR or PAR	14 days	FP provided significantly greater relief than placebo for sinus pain and pressure (<i>P</i> ≤ 0.023) and nasal congestion (<i>P</i> ≤ 0.008)
	Kaiser et al. [62]	<i>N</i> = 299, ≥ 12 years SAR	2 weeks	Significantly greater improvements with FF vs. placebo in daily reflective total nasal symptom score (<i>P</i> < 0.001), daily reflective total ocular symptom score (<i>P</i> = 0.004) and patient-rated overall response to therapy (<i>P</i> < 0.001)

N, number of patients; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.

flow (*P* < 0.001 for all) [59]. In a subset of 76 Dutch patients, QOL scores evaluated using the Pediatric and Adolescent Rhinoconjunctivitis Quality of Life Questionnaires (PRQLQ and ARQLQ) for children aged 6–11 years and those older than 12 years of age, respectively, were improved, but the difference between budesonide and placebo when questionnaires were combined was not statistically significant, probably due to the relatively small sample size. Budesonide was well tolerated and showed an adverse events profile similar to that of the placebo nasal spray [59].

Triamcinolone acetonide nasal spray/beclomethasone dipropionate nasal spray. Three randomized, investigator-blind, parallel group trials of 3 weeks' duration compared triamcinolone acetonide aqueous nasal spray (220 mcg/day) with either fluticasone propionate nasal spray (200 mcg/day), each used once daily in the morning, or beclomethasone dipropionate nasal spray (336 mcg/day) used twice daily, in subjects at least ≥ 12 years of age with seasonal AR [56–58]. Both triamcinolone acetonide and fluticasone propionate groups showed similar improvements in total nasal symptoms and individual

nasal symptoms, and in Rhinoconjunctivitis Quality of Life Questionnaire scores (RQLQ), which measure the severity of symptoms and their impact on sleep, daily activities, emotions, and practical problems [56, 57]. A statistically significant difference between triamcinolone acetonide and fluticasone propionate in effect on RQLQ was not seen in either study, although treatment with these drugs led to statistically significant improvements in RQLQ from baseline. In the study with beclomethasone dipropionate, both INSs were equally effective in relieving symptoms of nasal stuffiness and discharge, itching, and total eye symptoms, and improving QOL (as measured by the RQLQ). However, patients preferred the odour and taste of triamcinolone acetonide [58]. All INSs studied in the three trials were safe and well tolerated and had comparable safety profiles [56–58].

Fluticasone propionate aqueous nasal spray. Randomized, double-blind, placebo-controlled trials have shown that fluticasone propionate (200 mcg/day) is effective and safe for the treatment of patients 4 years of age and older with seasonal or perennial AR [60, 61, 66]. A study of 22 days' duration in children and adolescents found that fluticasone propionate (200 mcg/day) but not loratadine (10 mg/day) significantly improved nasal symptoms (i.e. congestion, itching, rhinorrhea) ($P=0.03$), QOL (ARQLQ) ($P=0.03$), and verbal memory ($P<0.05$) [60]. A multi-centre study in symptomatic children aged 12 years and older with either seasonal or perennial AR found that, compared with placebo, treatment with fluticasone propionate once daily in the morning provided significantly greater relief of nasal congestion ($P\leq 0.008$) and associated sinus pain and pressure ($P\leq 0.023$) [61]. Fluticasone propionate was well tolerated, with an incidence of drug-related adverse events similar to that seen in placebo-treated patients [61].

Mometasone furoate nasal spray. Results of double-blind, placebo- and active-controlled, multi-centre studies have demonstrated that mometasone furoate nasal spray (200 mcg/day) once daily in the morning relieves symptoms of both perennial and seasonal AR in patients 12 years of age and older, including patients with severe rhinitis [54, 55]. Additionally, mometasone furoate nasal spray (100 or 200 mcg/day) once daily in the morning has demonstrated efficacy and both systemic and topical safety in relieving the symptoms of perennial and seasonal AR in patients 3–11 years of age [67, 68]. In subjects ≥ 12 years of age with seasonal AR, mometasone furoate was associated with significantly greater improvement in daytime ($P<0.01$) and night-time ($P=0.017$) total nasal symptoms, and daytime cough severity ($P<0.05$) compared with placebo [55]. Complete or marked relief of symptoms was reported by twice as many patients receiving mometasone furoate as placebo [55]. In a 3-month,

randomized, double-blind, parallel group study in 550 adults and children with perennial AR, mometasone furoate was significantly superior to fluticasone propionate (200 mcg/day) in relieving nasal congestion at day 29 and week 8 (percent improvements in nasal congestion scores from baseline of 53% vs. 45% and 56% vs. 48%, respectively; $P=0.04$ for both) [54]. Mometasone furoate was well tolerated in these trials, with no evidence of tachyphylaxis in the 3-month trial in subjects with perennial AR [54, 55].

Fluticasone furoate nasal spray. Fluticasone furoate was approved by the US Food and Drug Administration in April 2007 for the treatment of symptoms of seasonal and perennial AR in adults and children 2 years of age and older [69, 70].

In a 2-week clinical trial ($N=299$) with adults and adolescents aged ≥ 12 years with seasonal AR, fluticasone furoate (110 mcg/day) was associated with significantly greater improvements than placebo in the daily reflective total nasal symptom score ($P<0.001$), the daily reflective total ocular symptom score ($P=0.004$), and the overall RQLQ score ($P<0.001$) [62]. Seventy-three percent of fluticasone furoate-treated patients compared with 52% of placebo-treated patients reported improvement in their overall response to therapy, which was rated significant/moderate by 42% and 21%, respectively. Fluticasone furoate was well tolerated, the most common treatment-related adverse events being headache and epistaxis [62].

Immunotherapy

Long-term, beneficial effects have been reported with the use of subcutaneous immunotherapy (SIT) in studies of persons with AR, with and without asthma. In a study of 36 patients with AR or asthma to tree pollen, subjective symptom relief was maintained with SIT at the same level at 6 years as that reached at the end of 3 years. Decreases in skin sensitivity, as measured by skin prick tests, were also maintained in approximately 86% of AR patients and 68% of asthma patients. None of the AR patients developed asthma [71]. Another study involved 54 adults with tree-pollen-induced AR ($n=28$), asthma ($n=1$), or rhinitis and asthma ($n=25$). At the end of the 3-year immunotherapy period, symptom scores were reduced to one-tenth of the starting level, a reduction that enabled patients to tolerate 30 times more pollen than before treatment [72].

Whereas SIT has been the principal approach to immunotherapy in the treatment of AR, research has focused increasingly on sublingual immunotherapy (SLIT), which has the advantage of a treatment period limited to before and after the pollen season in those with seasonal AR. SLIT also may be the preferred formulation for immunotherapy in children, who may have an aversion or fear of injection. A study of 88 children, 5–15 years of age, with a history of tree-pollen-induced allergic rhinoconjunctivitis with or

without seasonal asthma for ≥ 2 years, concluded that treatment with SLIT led to significant reductions in symptoms ($P=0.01$) and medication scores ($P=0.04$) after 18 months. The treatment was well tolerated [73].

A limitation of immunotherapy is that it must be taken daily during the allergy season (and throughout the year for perennial AR) for optimal efficacy, thus making compliance a potential problem.

Managing allergic rhinitis comorbidities

The basic techniques for managing comorbidities associated with AR are essentially the same as those used for AR, i.e. allergen avoidance, selection of appropriate pharmaceuticals, and immunotherapy. Comorbidities are thought to arise when allergic triggers that affect the nose affect other areas associated with the airway, including the nasopharynx, lungs, and middle ear [11]. The INSSs have been shown to reduce the symptoms of AR as well as those of asthma, such as increased bronchial responsiveness to allergen challenge and exercise-induced bronchoconstriction [11]. Antihistamines can be effective in patients with mild intermittent AR and asthma. In patients with AR and bacterial rhinosinusitis, the combined use of INSSs and antibiotics has been shown to be more beneficial than the use of an antibiotic alone [11]. For otitis media, initial treatment involves selection of an appropriate antibiotic, e.g. amoxicillin. When AR is also present, allergen avoidance and antihistamines are recommended initially, followed by INSSs or intranasal cromolyn [74]. An antihistamine/decongestant combination may benefit patients with allergen-induced eustachian tube dysfunction, thus potentially alleviating symptoms of otitis media with effusion [11, 42].

Systemic corticosteroids have also been found to relieve symptoms of AR, as well as the swelling and inflammation associated with comorbidities of AR such as eustachian tube dysfunction, rhinosinusitis, and asthma [11]. An additional systemic treatment for patients with AR, with or without asthma, is immunotherapy [11, 75]. Immunotherapy may also be useful in reducing symptoms involving other organ systems and is usually considered when environmental controls and pharmacotherapy have been ineffective [11].

Discussion and conclusions

AR is a common health problem affecting at least one-third of adults and children in the United States, but is often undiagnosed or inadequately treated/untreated. Many patients do not seek medical treatment for symptoms of AR, and others self-medicate with OTC medications, often sedating antihistamines. These agents are associated with decreased performance at work or school, and significantly increase the risk of accidental injuries. Lack of or inadequate treatment of AR can substantially

impair overall QOL by causing fatigue, headache, sinus pain, cognitive impairment and/or inability to concentrate, and other problems. Children with AR have more frequent absences from school and may experience behavioural problems. Comorbid conditions associated with AR, such as asthma, otitis media, and lymphoid hypertrophy with OSA, can be especially problematic in children when their AR is not treated.

People with AR describe nasal congestion as the most bothersome rhinitis symptom and the one they most want to prevent because it disrupts sleep, resulting in diminished daytime performance, and is a factor in OSA and habitual snoring. Effective treatment of AR is related to accurate diagnosis. As a first step towards controlling congestion, a congestion screening tool, the Congestion Quantifier, may help patients determine if nasal congestion is a significant component of their AR symptoms and help guide treatment decisions. The most potent agents currently available for the treatment of AR are INSSs, two of which, mometasone furoate and fluticasone furoate, are approved for use in children as young as 2 years of age. Numerous clinical studies in children and adults have demonstrated that by reducing rhinitis symptoms, particularly nasal congestion, INSSs also improve QOL in individuals with AR.

References

- 1 Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; **108** (Suppl. 5): S147–334.
- 2 Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. *Thorax* 1991; **46**:895–901.
- 3 Wuthrich B, Schindler C, Leuenberger P, Ackermann-Liebrich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss Study on Air Pollution and Lung Diseases in Adults. *Int Arch Allergy Immunol* 1995; **106**:149–56.
- 4 U.S. Department of Health and Human Services. Agency for Healthcare Research and Quality. Management of Allergic and Nonallergic Rhinitis: Summary. Evidence Report/Technology Assessment 54. May 2002.
- 5 Dykewicz MS, Fineman S. Executive summary of joint task force practice parameters on diagnosis and management of rhinitis. *Ann Allergy Asthma Immunol* 1998; **81**:463–8.
- 6 Crystal-Peters J, Crown WH, Goetzel RZ, Schutt DC. The cost of productivity losses associated with allergic rhinitis. *Am J Manag Care* 2000; **6**:373–8.
- 7 Collins JG. Prevalence of selected chronic conditions: United States, 1990–1992. National Center for Health Statistics. *Vital Health Stat* 10 1997; **194**:1–89.
- 8 Nolte H, Nepper-Christensen S, Backer V. Unawareness and undertreatment of asthma and allergic rhinitis in a general population. *Respir Med* 2006; **100**:354–62.

- 9 Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99 (Part 1):22–7.
- 10 Bachert C, Vignola AM, Gevaert P, Leynaert B, Van Cauwenberge P, Bousquet J. Allergic rhinitis, rhinosinusitis, and asthma: one airway disease. *Immunol Allergy Clin North Am* 2004; 24:19–43.
- 11 Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol* 1997; 99:S773–80.
- 12 Skoner DP. Complications of allergic rhinitis. *J Allergy Clin Immunol* 2000; 105:S605–9.
- 13 Lack G. Pediatric allergic rhinitis and comorbid disorders. *J Allergy Clin Immunol* 2001; 108:S9–15.
- 14 Lamb CE, Ratner PH, Johnson CE *et al.* Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. *Curr Med Res Opin* 2006; 22:1203–10.
- 15 Bousquet J, Van Cauwenberge P, Bachert C *et al.* Requirements for medications commonly used in the treatment of allergic rhinitis. *Allergy* 2003; 58:192–7.
- 16 Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001; 108:S2–8.
- 17 Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. *Clin Ther* 2004; 26:1876–89.
- 18 Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. *J Allergy Clin Immunol* 2000; 105:S616–21.
- 19 Peroni DG, Piacentini GL, Alfonsi L *et al.* Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy* 2003; 33:1349–54.
- 20 Juniper EF. Measuring health-related quality of life in rhinitis. *J Allergy Clin Immunol* 1997; 99:S742–9.
- 21 Meltzer EO, Nathan RA, Selner JC, Storms W. Quality of life and rhinitic symptoms: results of a nationwide survey with the SF-36 and RQLQ questionnaire. *J Allergy Clin Immunol* 1997; 99:S815–9.
- 22 Marshall PS, Colon EA. Effects of allergy season on mood and cognitive function. *Ann Allergy* 1993; 71:251–8.
- 23 Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. *Ann Allergy Asthma Immunol* 2000; 84:403–10.
- 24 Burton WN, Conti DJ, Chen CY, Schultz AB, Edington DW. The impact of allergies and allergy treatment on worker productivity. *J Occup Environ Med* 2001; 43:64–71.
- 25 Berger WE. Allergic rhinitis in children: diagnosis and management strategies. *Paediatr Drugs* 2004; 6:233–50.
- 26 Lierl MB. Allergy of the upper respiratory tract. In: Lawlor GJ Jr, Fischer TJ, Adelman DC, eds. *Manual of allergy and immunology*, 3rd Edn. Boston, MA: Little, Brown and Company, 1995; 94–111.
- 27 Bresolin D, Shapiro PA, Shapiro GG, Chapko ML, Dassel S. Mouth breathing in allergic children: its relationship to dentofacial development. *Am J Orthod* 1983; 83:334–40.
- 28 Walker S, Khan-Wasti S, Fletcher M *et al.* Hayfever is associated with a significant detrimental impact on exam performance in UK teenagers: case-control study. *Clin Exp Allergy* 2006; 36:1209.
- 29 Richards W. Asthma, allergies, and school. *Pediatr Ann* 1992; 21:575–85.
- 30 Savolainen S. Allergy in patients with acute maxillary sinusitis. *Allergy* 1989; 44:116–22.
- 31 Mion O, del Mello JF Jr, Lessa MM, Goto EY, Miniti A. The role of rhinitis in chronic otitis media. *Otolaryngol Head Neck Surg* 2003; 128:27–31.
- 32 Grossman J. One airway, one disease. *Chest* 1997; 111:11–6S.
- 33 Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997; 99:S781–6.
- 34 Fireman P. Otitis media and eustachian tube dysfunction: connection to allergic rhinitis. *J Allergy Clin Immunol* 1997; 99:S787–97.
- 35 Lazo-Saenz JG, Galvan-Aguilera AA, Martinez-Ordaz VA, Velasco-Rodriguez VM, Nieves-Renteria A, Rincon-Castaneda C. Eustachian tube dysfunction in allergic rhinitis. *Otolaryngol Head Neck Surg* 2005; 132:626–9.
- 36 Nguyen LHP, Manoukian JJ, Sobol SE *et al.* Similar allergic inflammation in the middle ear and the upper airway: evidence linking otitis media with effusion to the united airways concept. *J Allergy Clin Immunol* 2004; 114:1110–5.
- 37 Modrzynski M, Zawisza E. An analysis of the incidence of adenoid hypertrophy in allergic children. *Int J Pediatr Otorhinolaryngol* 2007; 71:713–9.
- 38 Modrzynski M, Zawisza E. The influence of birch pollination on adenoid size in children with intermittent allergic rhinitis. *Int J Pediatr Otorhinolaryngol* 2007; 71:1017–23.
- 39 McColley SA, Carroll JL, Curtis S, Loughlin GM, Sampson HA. High prevalence of allergic sensitization in children with habitual snoring and obstructive sleep apnea. *Chest* 1997; 111:170–3.
- 40 Young T, Finn L, Kim H, for the University of Wisconsin Sleep and Respiratory Research Group. Nasal obstruction as a risk factor for sleep-disordered breathing. *J Allergy Clin Immunol* 1997; 99:S757–62.
- 41 Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. Findings from a large online survey. *Treat Respir Med* 2005; 4:439–46.
- 42 Shedden A, Iezzoni D. Congestion and its impact on sleep in individuals with allergic rhinitis. Poster presented at the European Academy of Allergology Asthma and Immunology; 10–16 June 2006, Vienna, Austria.
- 43 Krouse J, Stull D, Naclerio R *et al.* Development of a self-report screener for congestion. Presented at the European Academy of Allergology and Clinical Immunology; 10–16 June 2006, Vienna, Austria.
- 44 Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2001; 108:S45–53.
- 45 Schoenwetter WF, Dupclay L Jr, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. *Curr Med Res Opin* 2004; 20:305–17.
- 46 Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol* 1999; 103:54–9.
- 47 American Academy of Allergy, Asthma and Immunology (AAAAI). The allergy report: overview of allergic diseases: diagnosis, management, and barriers to care, 2000, <http://www.Theallergyreport.org/>
- 48 Stokes J, Fenstad E, Casale TB. Managing impairment in patients with allergic rhinitis. *Allergy Asthma Proc* 2006; 27:12–6.
- 49 Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993; 71:121–6.

- 50 Fireman P. Treatment of allergic rhinitis: effect on occupation productivity and work force costs. *Allergy Asthma Proc* 1997; 18:63–7.
- 51 Weiler JM, Bloomfield JR, Woodworth GG *et al.* Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa Driving Simulator. *Ann Intern Med* 2000; 132:354–63.
- 52 Gilmore TM, Alexander BH, Mueller BA, Rivara FP. Occupational injuries and medication use. *Am J Ind Med* 1996; 30:234–9.
- 53 Finkle WD, Adams JL, Greenland S, Melmon KL. Increased risk of serious injury following an initial prescription for diphenhydramine. *Ann Allergy Asthma Immunol* 2002; 89:244–50.
- 54 Mandl M, Nolop K, Lutsky B, participants in the 194-079 Study Group. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. *Ann Allergy Asthma Immunol* 1997; 79:370–8.
- 55 Gawchik S, Goldstein S, Prenner B, John A. Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. *Ann Allergy Asthma Immunol* 2003; 90:416–21.
- 56 Berger WE, Kaiser H, Gawchik SM *et al.* Triamcinolone acetonide aqueous nasal spray and fluticasone propionate are equally effective for relief of nasal symptoms in patients with seasonal allergic rhinitis. *Otolaryngol Head Neck Surg* 2003; 129:16–23.
- 57 Gross G, Jacobs RL, Woodworth TH, Georges GC, Lim JC. Comparative efficacy, safety, and effect on quality of life of triamcinolone acetonide and fluticasone propionate aqueous nasal sprays in patients with fall seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2002; 89:56–62.
- 58 Lumry W, Hampel F, LaForce C, Kiechel F, El-Akkad T, Murray JJ. A comparison of once-daily triamcinolone acetonide aqueous and twice-daily beclomethasone dipropionate aqueous nasal sprays in the treatment of seasonal allergic rhinitis. *Allergy Asthma Proc* 2003; 24:203–10.
- 59 Fokkens WJ, Cserh ti E, Lopes dos Santos JM *et al.* Budesonide aqueous nasal spray is an effective treatment in children with perennial allergic rhinitis, with an onset of action within 12 hours. *Ann Allergy Asthma Immunol* 2002; 89: 279–84.
- 60 Bender BG, Milgrom H. Comparison of the effects of fluticasone propionate aqueous nasal spray and loratadine on daytime alertness and performance in children with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2004; 92:344–9.
- 61 Ratner PH, Howland WC III, Jacobs RL *et al.* Relief of sinus pain and pressure with fluticasone propionate aqueous nasal spray: a placebo-controlled trial in patients with allergic rhinitis. *Allergy Asthma Proc* 2002; 23:259–63.
- 62 Kaiser HB, Naclerio RM, Given J, Toler TN, Ellsworth A, Philpot EE. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; 119:1430–7.
- 63 Schenkel E, LaForce C, Gates D. Mometasone furoate nasal spray in seasonal allergic rhinitis: effective in relieving ocular symptoms. *Allergy Clin Immunol Int – J World Allergy Org* 2007; 19:50–3.
- 64 Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H₁ receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998; 317: 1624–9.
- 65 Mintz M, Garcia J, Diener P, Liao Y, Dupclay L, Georges G. Triamcinolone acetonide aqueous nasal spray improves nocturnal rhinitis-related quality of life in patients treated in a primary care setting: the quality of sleep in allergic rhinitis study. *Ann Allergy Asthma Immunol* 2004; 92:255–61.
- 66 GlaxoSmithKline. *Flonase [package insert]*. GlaxoSmithKline, Research Triangle Park, NC, 2006.
- 67 Schenkel EJ, Skoner DP, Bronsky EA *et al.* Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics* 2000; 105:e22.
- 68 Meltzer EO, Berger WE, Berkowitz RB *et al.* A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999; 104:107–14.
- 69 U.S. Food and Drug Administration, Center for Drug Evaluation and Research. CDER Drug and Biologic Approvals for Calendar Year 2007, updated through 30 April 2007. Available at: <http://www.fda.gov/cder/rdmt/InternetNDA07.htm> (Accessed 15 June 2007).
- 70 GlaxoSmithKline *Veramyst [package insert]*. GlaxoSmithKline, Research Triangle Park, NC, 2007.
- 71 Jacobsen L, Petersen BN, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts. *Allergy* 1997; 52:914–20.
- 72 Petersen BN, Janniche H, Munch EP *et al.* Immunotherapy with partially purified and standardized tree pollen extracts. I. Clinical results from a three-year double-blind study of patients treated with pollen extracts either of birch or combinations of alder, birch and hazel. *Allergy* 1988; 43:353–62.
- 73 Valovirta E, Jacobsen L, Ljorring C, Koivikko A, Savolainen J. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. *Allergy* 2006; 61:1177–83.
- 74 Fireman P. Otitis media and its relation to allergic rhinitis. *Allergy Asthma Proc* 1997; 18:135–43.
- 75 Kirtsreesakul V, Naclerio RN. Role of allergy in rhinosinusitis. *Curr Opin Allergy Clin Immunol* 2004; 4:17–23.