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REVIEW

Quality of life and control of allergic rhinitis in patients from regions beyond western Europe and the United States

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Summary

There is comparatively little information on health-related quality of life (HRQoL) in subjects with allergic rhinitis (AR) or allergic rhinoconjunctivitis (AR/C) in countries beyond western Europe and North America. The primary aim of this investigation was therefore to review and assess the information in the public domain on HRQoL in AR/C patients from diverse regions of the world, represented by different countries, including Argentina, Australia, Brazil, Russia, Singapore, South Africa and Turkey. Second, in view of the absence of a standardized definition for 'AR control', the review aimed to determine whether a working definition of AR/C can be inferred from validated tests or other instruments documented to date. Despite the comparatively low number of studies, this review demonstrated that overall the symptoms of AR/C impair the HRQoL of patients in these regions by adversely impacting sleep, daily activities, physical and mental status and social functioning, similar to that demonstrated in much larger numbers of studies of AR/C patients in Europe and the United States. Furthermore, the findings of the review suggest that 'overall' control of the disease should encompass reduction of nasal and ocular symptoms, as well as improvements in HRQoL, comorbid conditions and cognition. Although some instruments are currently available for measuring control of AR, none are capable of assessing all these aspects, emphasizing the need to develop appropriate new instruments.

Keywords allergic rhinitis, allergic rhinoconjunctivitis, control, diverse regions, health-related quality of life
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Introduction

Allergic rhinitis/allergic rhinoconjunctivitis (AR/C) is a common chronic respiratory disorder, which is estimated to affect up to 40% of the population worldwide [1]. Epidemiologic evidence from Europe and the United States has indicated that the prevalence of AR/C ranges between 23% and 30% in Europe [2, 3] and between 12 and 30% in the United States [4]. Data from regions beyond Europe and the United States, however, have indicated that there is greater diversity in the prevalence of AR/C within and between regions including Africa [7.2–54.1%], Asia Pacific region [1.6–47.2%], Australia [12–41.3%], Eastern Europe/Russia [3.2–12.8%], Middle East [7.4–45.2%], South America [5–74.6%] and South East Asia [5.5–44.3%][5]. It is likely that the large variation in prevalence of AR/C in these regions is a consequence of both conventional and non-conventional risk factors, particularly increased exposure to a variety of indoor antigens and air pollutants, associated with industrialization and adoption of a 'westernized lifestyle' with more time spent indoors in better insulated and heated housing, a move away from a traditional diet, change in furnishings within the home, etc. Although it is presently not clear whether there are differences in the severity and control of allergic rhinitis between these regions and Europe/United States, it is likely that AR/C manifestations and

patients' complaints may differ in different parts of the world, due to a variety of reasons. For example 'non-seasonality' and the perennial nature of particularly the indoor allergens (especially dust mites) in the tropics are likely to lead to presentation of predominantly persistent symptoms in the majority of patients from the tropics and areas with long dry summers, compared with Europe and the United States. In addition, as the allergens and their 'subspecies' are different in the regions beyond Europe and the United States, immunotherapy with the 'European/American' vaccines (e.g. Blomia for mites and other grass pollens in the panicoideae subfamily) is likely to be different, inappropriate or ineffective in patients from these regions. Furthermore, 'control' may be more difficult due to lack of access to newer medications (non-sedating antihistamines, vaccines, etc.) and accessibility to allergy specialists and allergy tests in many regions outside of Europe and the United States.

Despite the availability of evidence-based treatment international guidelines such as the WHO-sponsored ARIA guidelines [6], evidence suggests that GPs often misdiagnose the severity and impact of the disease over quality of life and therefore may treat their patients inappropriately, leading to low patient satisfaction and compliance [7–10]. This situation is further compounded by the fact that presently there is no clear definition of what might constitute total 'AR control', analogous to that available for asthma [11]. Indeed, while the control of asthma [11] and chronic obstructive pulmonary disease (COPD) [12] are being stressed by evidence-based guidelines, the control of rhinitis has not been addressed at all in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [1, 6]. Furthermore, only about half of the patients appear to seek medical care because they underestimate the disease or manage it with inadequate expectancy about the results of the treatment [1]. Also, in many of the regions included in the present investigation, availability of health care, especially appropriately trained allergists, is lacking and affordability of EBM best medications is much more difficult than in Europe and the United Sates.

Although AR/C is not a life-threatening condition, it is increasingly recognized that the symptoms of AR/C often adversely impact both work and quality of life (QoL; i.e. a patient's subjective perception of their overall well-being, in terms of all physical, emotional/psychological, social, as well as cultural and environmental aspects of the individual's life) of the affected individuals and impose a significant health and socio-economic burden on the individual and the society [13–16]. A recent editorial by van Wijk [17] has suggested that although attention to the burden of AR and asthma is a major step forward in acknowledging the patient perspective, awareness by itself is unlikely to lead to better management of affected individuals. Current consensus among many experts in the field indicates that it is essential to consider 'the subjective dimension of diseases in order to have a more global and coherent vision about the patient and the effects of the whole healthcare process' [18]. It has been suggested that Patient-reported outcomes (PROs; involving all health-related issues such as symptoms, HRQoL, illness perception, satisfaction with or adherence to treatment, health status, well-being, work productivity, as well as control of disease) reported directly by the patients, without interpretation by physicians or others about how they function or feel in relation to a health condition and its therapy, should be used to evaluate the effect of a medicinal product [18–21]. The European Medicines Agency (EMA) [21] has suggested that in non-life-threatening chronic disease, results based on PROs could provide a useful indication for the choice of drug, when two or more drugs are shown to have similar efficacy. Although several tools are available for assessing different PROs, many of these have not been used extensively in patient suffering from allergic rhinitis and/or asthma and need to be validated further in these patient groups [19].

Health-related quality of life (HRQoL) is now recognized by the Global Allergy and Asthma European Network (GA^2LEN) as one of the most important PROs in patients with rhinitis and asthma [19], particularly as it is a subjective measure of a patient's perception of the impact of his/her disease and its treatment(s) on his/her daily life, physical- psychological- and social-functioning, and general well-being [21]. Several validated instruments are currently available and extensively used for measuring HRQoL in these patient groups; however, these instruments are somewhat limited in that they have generally been designed for clinical trials and analysis at a group level in specified patient populations. Thus, while assessment of HRQoL may provide an estimate of a therapeutic effect under experimental conditions, it is unlikely to provide an accurate/detailed picture applicable to the real-life situation. In this regard, a population-based study of factors affecting HRQoL in patients with rhinitis has demonstrated that in addition to disease symptoms severity, psychosocial factors such as distress and patient-perceived control of disease were directly correlated with the degree of HRQoL [22]. These findings suggest that such factors are a potential source of substantial variability in HRQoL among adults with rhinitis and need to be considered for appropriate management of disease in affected individuals. In view of the specificity and importance of assessing HRQoL in rhinitis and asthma patients, the GA^2LEN taskforce position paper on PROs and HRQoL [19] has recently recommended that use of

specific questionnaires should be preferred to the use of generic tools. Several aspects should be considered in the choice of an instrument, including the disease target (i.e. asthma, rhinoconjunctivitis, rhinosinusitis, and concomitant asthma and rhinitis), the population target (i.e. adult, adolescent, paediatric), methods of administration and format (i.e. self/guardian/carer-administered, interview, telephone administered), availability in language of population investigated, dimensions investigated (i.e. specific domains) and scale/scoring system (e.g. 3- to 7-point Likert scales, visual analogue scales, total and/or single domain scores). More recently, van Wijk [17] has suggested that introduction of questionnaires aimed at controlling disease is likely to add another dimension to assessing HRQoL in patients with respiratory diseases and shift attention from assessing symptom severity to assessing the adequacy of management.

The majority of information on QoL/HRQoL in AR/C patients, and indeed on the prevalence and the triggers/factors responsible for the manifestation of AR, is well documented for patients from Europe and the United States. In contrast, there is a comparatively smaller, but gradually increasing, amount of information on QoL/HRQoL in AR/C patients from countries beyond western Europe and North America. The aim of this investigation was therefore to review and assess the information in the public domain on QoL/HRQoL in AR/C patients from diverse regions of the world, represented by a selected group of countries, including Argentina, Australia, Brazil, Russia, Singapore, South Africa and Turkey. Second, the review aimed to determine whether a standardized definition of AR/C 'control' currently exists or can be inferred from validated tests or other instruments that have been documented to date.

Methods

Search strategy

The PubMed, a comprehensive biomedical literature database providing access to MEDLINE, life science journals and online books, was used to conduct a comprehensive literature search for articles documenting the QoL/HRQoL in allergic rhinitis patients, published up to August 2011. Citations for relevant articles were identified using *"allergic rhinitis"* and *"allergic rhinoconjunctivitis"* as the primary search terms in combination with *"quality of life"* and the country of interest (*"Argentina", "Australia", "Brazil", "Russia", "Singapore", "South Africa"* or *"Turkey"*) as secondary search terms. Because of the diversity in study design and experimental methods and instruments employed for assessing and documenting the QoL/HRQoL in AR/C patients in the different regions of interest, the quality of the articles was not assessed according to any predetermined criteria for inclusion in the review. Thus, potential articles were initially identified by the title and/or the specific study details provided in the abstracts and only relevant articles published as full papers in English in peer-reviewed journals were selected for further review and inclusion, as described before [5].

In the absence of a standardized definition of 'AR control', a separate literature search was also conducted of any studies documenting *"allergic rhinitis control"* as a specific outcome measure in clinical trials, using combinations of "*allergic rhinitis"*, *"disease control", "symptoms control", "control"* and *"uncontrolled symptoms"*, as the primary search terms, in an attempt to formulate a working definition of AR control.

Results

Overall 1170 citations were identified using the combination of the primary search terms with quality of life, of which 60 articles were associated with the different countries of interest. Further evaluation of the articles highlighted 28 articles [23–50], which were considered to be suitable for inclusion in the review (Table 1).

Quality of life in AR/C patients from diverse countries beyond western Europe and North America

Several studies have investigated the quality of life of patients suffering from AR or AR/C in the countries reviewed in this investigation, of which the vast majority have been performed in patients from Australia [23–30] and Turkey [40–50]. Although the standardized or translated versions of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and the Paediatric Rhinitis Quality of Life Questionnaire (PRQLQ) have been employed as the instruments of choice in the majority of studies for assessing the HRQoL in adult and paediatric patient cohorts, respectively, the generic SF-36 questionnaire has also been employed in several studies [26, 34, 35, 40, 44, 47–49]. More recent studies have employed continuous actigraphy [23] and all-night polysomnography [47] to assess sleep quality, duration and efficiency, as well as the Epworth Sleepiness Scale (ESS) [41, 47], a self-administered questionnaire for measuring a subject's general level of daytime sleepiness [51,52]. Assessment of AR-associated sleep disturbance may be important because although both sleep and HRQoL have shown to be independently impaired in subjects with AR, a large epidemiological survey from Spain has recently provided evidence that poor sleep quality, particularly in patients with more severe disease, was correlated with HRQoL deterioration in these individuals [53].

Table 1. Citations identified using the combination of the primary search terms with quality of life, which were also associated with the countries of interest

Country	Subjects	Study design/Method for assessing QoL measures	Main findings	Reference (n)
Australia	1060 subjects (age 20–49 yrs) with self-reported moderate to severe symptoms of AR 10 HDM-allergic PAR subjects and 10 healthy control subjects 47 subjects (age > 18 years) with IAR: (Group A = 26 with self-set AR management strategies/goals; Group B = 21 with pharmacist-assisted AR management strategies/goals) 37 HDM-allergic PAR subjects and 19 healthy control subjects 65 SAR patients (33 treated with Chinese herbal drug preparation and 32 with placebo) 55 SAR patients (28 treated with Chinese herbal drug preparation and 27 with placebo) 145 Olympic and Paralympic athletes with SAR/C	Online survey to assess QoL using a questionnaire comprising 24 questions Continuous actigraphy to assess sleep quality (sleep onset, sleep duration and sleep fragmentation) and diary records of sleep quality Community pharmacy-based parallel-group study, with random allocation of participating pharmacies. QOL assessed using mini-RQLQ Prospective parallel-group study Symptom severity and QoL assessed by SF-36 and RQLQ over 1-year period R/DB/PC study to investigate the effect of acupuncture twice a week for 8 weeks plus a Chinese herbal drug preparation or placebo, on symptom severity and RQLQ scores R/DB/PC study to investigate the effect of treatment for 8 weeks with a Chinese herbal drug preparation or placebo, on symptom severity and RQLQ scores Community-based studies to investigate the effect of SAR/C and treatment with intranasal budesonide for 8 weeks on symptoms and RQLQ scores	Symptoms affected mood in 97% of patients, daily activity in 91% patients and relationships in 82% patients Significantly increased fragmentation index value in PAR subjects (i.e. reduced sleep quality and increased sleep disturbance, which may impair QoL) compared with controls Significant improvements in symptom severity and quality of life scores of both groups, however, symptom severity scores improved more in Group B Nasal symptom scores consistently high in PAR subjects and their QoL scores (for nose and eye symptoms, fatigue, thirst, tiredness, productivity and concentration) worse than controls, over the entire course of study No significant differences between treatments in improvement of symptom or RQLQ scores. Severity of nasal and non-nasal symptoms significantly decreased and RQLQ scores significantly improved in patients treated with the herbal drug preparation, compared with placebo QoL of significantly impaired in athletes with SAR/C, compared with non-allergic athletes. Budesonide significantly improved symptoms, RQLQ scores and performance in athletes with SAR/C	Sharp TJ, et al., [23] Rimmer J, et al., [24] O'Connor, et al., [25] Downie SR, et al., [26] Xue CC, et al., [27] Xue CC, et al., [28] Katelaris CH, et al., [29] Katelaris CH, et al., [30]
Brazil	1088 adults and 457 children from 22,012 households across Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Peru and Venezuela 57 teenagers with perennial allergic rhinitis	Population-based survey to assess the prevalence of general practice physician or otolaryngologist diagnosed nasal allergies and their impact on QoL To assess reproducibility and responsiveness of Brazilian version of RQLQ	Approximately 7 % of the population suffered from nasal allergies, which were seasonal or intermittent in 2 of 3 respondents. Symptoms of nasal allergy affected productivity and sleep and impaired QoL in majority of subjects affected The adapted questionnaire is reproducible and valid for use in longitudinal studies, but requires confirmation in other studies	Neffen H, et al., [31] Nascimento Silva M, et al., [32]
Russia	2- to 12-year-old children enrolled from 424 primary-care/specialist allergy clinics across Bulgaria, India, Portugal, Romania, Russia, South Korea and Spain	Observational Survey in Children with Allergic Rhinitis (OSCAR), to assess overall efficacy and tolerability of oral antihistamines	Levocetirizine and fexofenadine perceived by parents and physicians to produce significantly higher treatment satisfaction than the majority of the other antihistamines, with respect to overall efficacy, tolerability and impact on the child's sleep and school activities	Ferrer M, et al., [33]

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Table 1 (continued)

Country	Subjects	Study design/Method for assessing QoL measures	Main findings	Reference (n)
Singapore	43 newly diagnosed PAR subjects and 44 controls	Prospective interviewer-administered studies to assess and validate the psychometric properties of the RQLQ and SF-36 QoL instruments	Both SF-36 and RQLQ discriminated rhinitis patients from controls, but SF-36 was poor for detecting changes in QoL. Each instrument measured only non-overlapping halves of the measurable HRQL and should therefore be employed together for complete assessment of the health-related QoL in patients with PAR	Leong KP, et al., [34] and [35]
South Africa	10,215 schoolchildren aged 13–14 years 1181 AR patients, aged 5–67 years 306 children (age 6–12 years) with PAR (154 treated with levocetirizine 5 mg/day and 152 with placebo for 4 weeks) 253 adults and adolescents (age 12–75 years) with SAR/PAR (170 treated with triamcinolone 220 μg/day and 83 with placebo for 4 weeks)	Cross-sectional study using the standardized ISAAC study design, to assess time trends in prevalence and impact of allergic disease, including AR and AR/C Population-based questionnaire study to assess a variety of AR-associated factors, including health-related QoL R/DB/PC multi-centre studies to investigate the effect of treatment on symptoms, and health-related QoL measured using the PRQLQ in children and RQLQ in adults with PAR	The 12-month prevalence of AR and AR/C symptoms increased by 8.1% and 6.6%, respectively, over a 7-year period. Limitation of daily activity due to nasal symptoms increased by 15.5% over same period Symptoms affected sleep in 76.6% of sufferers (with sleep in 37.2% being affected every night). Over half the patients were concerned that AR restricted their social activities Levocetirizine significantly improved total nasal symptoms scores and PRQLQ scores in children compared with placebo. Triamcinolone significantly improved RQLQ scores for activities, sleep, practical and emotional problems, nasal and eye symptoms and overall scores in adults with PAR compared with placebo	Zar HJ, et al., [36] Green RJ, et al., [37] Potter PC, et al., [38] and [39]
Turkey	55 adult subjects with AR 132 patients (69 with AR and 63 with non-AR), mean age 33.14 years 70 patients with PAR (46 treated with montelukast 10 mg/day and 24 treated with placebo for 4 weeks) 100 subjects (age 18–52 years) with AR not controlled with anti-allergic medication and 34 healthy control subjects 55 adults (age 18–69 years) with AR and 102 children (age 6–16 years) with AR. 31 children with AR and 18 healthy controls (age 5–15 years) 48 adults (mean age 39.6 ± 12.7 years); 25 with AR and 23 with NAR 323 patients (mean age 31.8 ± 12.6 years); 205 with AR and 118 with NAR	Randomized, parallel-group study to assess the effect of intranasal steroid (INS) or radiofrequency turbinoplasty (RFT) therapy on QoL measured by RQLQ Randomized, parallel-group study to assess the effect of azelastine versus triamcinolone nasal sprays on sleep and QoL measured by ESS and SF-36, respectively R/DB/PC study to investigate the effect of montelukast on health-related QoL measured using the RQLQ Prospective parallel-group study to investigate the effect of intranasal phytotherapy (combination of UV-A, UV-B, and visible light) three times a week for 2 weeks, on QoL, measured using the RQLQ To assess validity and reliability of Turkish versions of RQLQ and mini-RQLQ in adults and PRQLQ in children	Both therapies significantly improved RQLQ scores after 1 year of treatment; however, RFT led to greater improvements in nasal congestion and nasal resistance than INS Both azelastine and triamcinolone significantly improved the ESS score and each SF-36 domain score, irrespective of rhinitis aetiology Montelukast monotherapy significantly improved RQLQ scores for sleep, practical problems, nasal problems and activities limited by nose or eye symptoms, as well as overall score by end of treatment, compared with placebo Phytotherapy significantly improved all seven RQLQ domain scores, namely sleep, non-nasal eye symptoms, practical problems, nasal symptoms, eye symptoms, activities that have been limited by nose or eye symptoms, and emotional function after 1 and 3 months, compared with baseline	Gunhan K, et al., [40] Kalpaklioğlu AF, et al., [41] Cingi C, et al., [42] Cingi C, et al., [43] Yüksel H, et al., [44] and 2009a [45] Yüksel H, et al., [46] Kalpaklioğlu AF, et al., [47]

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Table 1 (continued)

Country	Subjects	Study design/Method for assessing QoL measures	Main findings	Reference (n)
	316 patients (age 10–69 years); with AR (232), asthma [40],or AR + asthma [44] 95 AR patients (25 treated with mometasone; 25 with mometasone + desloratadine; 25 with mometasone + montelukast; 20 with placebo)	To investigate the relationship between clinical parameters and eosinophilic cationic protein (ECP) with QoL, measured by PRQLQ Observational study to assess impact of rhinitis on sleep and QoL, using ESS and SF-36, respectively. Sleep also evaluated by all-night polysomnography A retrospective study involving 478 consecutive and unselected patients referred to an outpatient tertiary clinic, of whom 323 with rhinitis were assessed for general features of AR and NAR, as well as QoL, using SF-36 A prospective study involving 481 patients referred to outpatient clinic for allergy or asthma. Eligible patients diagnosed with either or both diseases and assessed for QoL using SF-36 Open, placebo-controlled, parallel-group study to assess effect of INS (mometasone) monotherapy with combined (mometasone + desloratadine/ montelukast) therapy on symptoms and QoL measured by RQLQ	Total RQLQ and mini-RQLQ scores significantly correlated with total four symptoms score (T4SS) and all SF-36 domains, except physical-functioning domain. Similarly, PRQLQ domain and total scores significantly correlated with T4SS Total clinical symptom score and disease duration significantly correlated with total PRQLQ score, but nasal lavage/serum ECP levels not correlated with PRQLQ total or domain scores Greater number of NAR patients had > 10 ESS scores than AR patients, with obstructive sleep apnoea syndrome (OSAS) detected in 83% and 36% NAR and AR patients, respectively. All 8 SF-36 subscales significantly impaired in both groups, compared with normal Turkish general population. Polysomnography also showed significantly shorter sleep duration and sleep efficiency in NAR patients compared with AR patients Symptoms of rhinitis more seasonal in AR patients and more perennial in NAR patients. Conjunctivitis and sinusitis were more prominent in AR than NAR group. Impairment of QoL similar in both groups; mean scores of the SF-36 subscales, except physical functioning, higher in AR than in NAR patients, although not statistically significant. Similarly, physical and mental component scores (PCS and MCS, respectively) not significantly different QoL was significantly lower in patients with asthma, with or without AR, than in patients with AR alone. Female gender, older age, increased BMI and less educational status were major determinants of impaired QoL All active treatments significantly better than placebo in terms of improving symptom and RQLQ scores, however, combination therapy with mometasone + desloratadine/montelukast significantly better than mometasone therapy alone	Kalpaklioğlu AF, et al., [48] Kalpaklioğlu AF, et al., [49] Pinar E, et al., [50]

AR = allergic rhinitis; AR/C = allergic rhinoconjunctivitis; ESS = Epworth Sleepiness Scale; HDM = house dust mite; IAR = intermittent allergic rhinitis; INS = intranasal steroid; ISAAC = International Study of Asthma and Allergies in Childhood; (mini-)RQLQ = (Mini-) Rhinoconjunctivitis Quality of Life Questionnaire; NAR = non-allergic rhinitis; PAR = persistent allergic rhinitis; PRQLQ = Paediatric Rhinoconjunctivitis Quality of Life Questionnaire; QoL = Quality of Life; RFT = radiofrequency turbinoplasty; SAR/C = seasonal allergic rhinoconjunctivitis; SF-36 = Medical Outcome Short Form-36 questionnaire; R/DB/PC = randomized, double-blind, placebo-controlled trial

Similarly, some studies have assessed the QoL of AR subjects using locally developed questionnaires appropriate to the region. The Allergies in Latin America cross-national survey [31] was specifically designed to assess the symptoms, impact and treatment of nasal allergies in eight Latin American countries (including, Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Peru and Venezuela). Over 22 000 households across the eight countries were interviewed over the telephone or in-person, according to standard protocols and questionnaires, which allowed screening for adults and children with a diagnosis of AR or nasal allergies and either symptoms or treatment in the past 12 months. Most of the interviews were conducted in urban areas due to the low telephone penetration and lack of interviewing infrastructure in rural Latin America, with the average interview lasting about 40 minutes. Overall, the study demonstrated that AR was highly prevalent in both Latin American children and adults, with 40–50% of all affected individuals indicating AR to moderately affect their daily life. Moreover, between 34% and 49% of adults and children reported AR to result in interference with or missing their work/school and declined work/school productivity, primarily due to sleep disturbances secondary to AR. More recently, the 'Allergies in Asia Pacific survey' [54, 55] has screened nearly 34,000 households in Australia, China, Hong Kong, Korea, Malaysia, the Philippines, Singapore, Taiwan and Vietnam, for individuals 4 years and older with a diagnosis of AR and symptoms/treatment in the past year, using standardized questionnaires. This survey also demonstrated that the prevalence of diagnosed AR was high in both adults (42%) and children (37%) in the Asia Pacific region [54], with >83% of the individuals with AR reporting some impact of the condition on their daily life [55]. Indeed, >45% of adults and 41% of children reported missing work/school or having their job/school performance diminished by their AR within the past 12 months. Moreover, between 59% and 71% of both adults and children reported sleep-related problems. In another study, Green and colleagues [37] employed a questionnaire specifically designed to screen AR and its impact on the QoL of affected individuals in five major cities (Bloemfontein, Cape Town, Durban, Johannesburg and Pretoria) across South Africa. The impact of AR on the QoL was identified according to two specific questions: (1) Do the symptoms of AR affect the quality of your sleep? and (2) Does rhinitis make you miserable? This study demonstrated that in 1181 patients aged 5–67 years, sleep was affected in 76.6% of sufferers, and in at least a third this was every night. Over 1000 respondents (85.2%) felt miserable due to AR and 53.1% of the patients were concerned that AR restricted their social activities. In a more recent study, Sharp and Seeto [23] conducted an online survey comprising 24 questions, to assess the psychosocial impact of morning symptoms amongst 1060 Australian adults with self-reported AR. The authors demonstrated that symptoms were more severe in the morning in 56% and affected mood in 97% of the patients. Moreover, the symptoms had some impact on their day ahead in 91% of the patients and a negative impact on relationships in 82% of patients.

Overall, despite the comparatively low number, these studies have nevertheless demonstrated that the symptoms of AR/C impair the QoL of patients in these regions by adversely impacting the patients' sleep, daily activities, physical and mental status and social functioning, as has been demonstrated in much larger numbers of studies of AR/C patients in Europe and the United States [1]. Moreover, it is interesting that in regions with the greatest populations, i.e. China and India, there is a marked lack or paucity of similar studies, resulting in a gaping lack of general as well as more specific comparative data across ethnicities and socio-economic groups.

'AR control'

There is a plethora of evidence that appropriate treatment decreases symptoms of AR [1, 56] and that treatment-related improvements in symptoms can be graded [57]. In marked contrast, there is little or no information on the effect of treatment on 'AR control', analogous to that available for asthma [11, 58]. Furthermore, to our knowledge there are no studies that have documented the use of 'allergic rhinitis control' as a specific outcome measure following treatment. It is likely that a major reason for the paucity of data on AR control is lack of a universally agreed definition of AR control, which is itself likely to be compounded by a variety of factors such as (i) the lack of information on how to assess control, (ii) whether control is similar/applicable for all patients irrespective of their disease status (i.e. intermittent/persistent AR or for seasonal/perennial AR) and (iii) whether achieving the pre-determined level of control would be relevant for the patient, useful for the physicians or cost-effective for health systems. In addition, it is clear that current alternatives are not sufficiently efficacious in controlling symptoms in about 20% of patients with severe persistent rhinitis [58]. Furthermore, there is some evidence which suggests that patients' perceived control of disease may influence their ability to deal with their disease and therefore partly determine health outcomes, such as management of symptoms/symptom severity and HRQoL [22]. Using an 8-item instrument, the 'Perceive Control of Rhinitis Questionnaire', Chen and colleagues [22] demonstrated that lower HRQoL in adults with rhinitis was correlated with not only greater symptom severity, poorer physical

functioning and psychological distress but also with less perceived control. Moreover, perceived control was found to be an independent predictor of HRQoL, similar to symptom severity and psychological distress. Similarly, there is evidence that patient satisfaction with therapy is associated with symptom control and HRQoL [59, 60]. Indeed, one recent study by an expert multidisciplinary Working Group on Allergic Rhinitis demonstrated that 60% of AR patients were often 'very interested' in finding a new medication and 25% were 'constantly' trying different medications to find one that 'worked' [59]. Moreover, dissatisfaction with treatment and a lack of effective communication between health care provider and patient lead to poor disease control, non-compliance and unhappiness in a significant portion of patients.

Working definition of AR control

There is little doubt that accurate assessment of rhinitis control is crucial in determining whether care is optimized and when treatment strategies need to be adjusted to achieve the best outcomes. Many new instruments, such as Rhinitis Control Assessment Test (RCAT) [61] and Control of Allergic Rhinitis and Asthma Test (CARAT) [62], which explore lower and/or upper airways symptoms, activities, sleep and treatment; specific visual analogue scales for global rhinitis symptoms [63, 64]; and other new questionnaires requiring further validation [65], have appeared recently. None have been widely adopted in a clinical setting, and in the absence of a standardized definition for AR control, there is no clear indication that 'AR control' is being measured directly. However, it is possible that a working definition of AR control may be formulated in a number of ways based on available data and different aspects of disease all of which are patient-reported and have specific advantages in everyday practice or for post hoc analyses of existing data from original clinical trials.

Definition based on analogy of GINA and National Heart, Lung, and Blood Institute (NHLBI) definition of asthma control. The concept of 'total' AR control may be thought of in terms of the degree to which the disease manifestations are being minimized and the goals of therapy are being achieved, similar to that described by the GINA [11] and NHLBI Expert Panel Report 3 definition of asthma control [58]. In this regard, AR control would mean the reduction or elimination of both nasal (sneeze, congestion, rhinorrhoea and nasal pruritus) and ocular symptoms (ocular itching/burning, tearing/watering and redness), which may affect the patient's sleep, interfere with/impair daily activity, and impact QoL and productivity. Furthermore, AR control would encompass the reduction or elimination of future risk for (i) development of nasal remodelling or any kind of damage to the nasal mucosa, particularly as few studies have addressed this aspect from the patient's point of view; (ii) olfaction abnormalities; (iii) development of upper airway comorbidities such as sinus disease and nasal polyps; (iv) development of otitis media with effusion and lower airways diseases or conditions such as asthma and (v) avoidance of side-effects of drugs such as cognitive impairment due to first-generation antihistamines, rhinitis medicamentosa due to local decongestives, etc.

Definition based on the recommendations of the American Joint Task Force on Practice Parameters. The American Joint Task Force on Practice Parameters (representing the American Academy of Allergy Asthma and Immunology, the American College of Allergy Asthma and Immunology and the Joint Council of Allergy Asthma and Immunology) has recently published the evidence-based updated guidelines on the diagnosis and management of rhinitis in adults (including pregnant women and the elderly) and children [56]. The guidelines recommend that 'Management and monitoring of rhinitis should be individualized and based on the spectrum, duration and severity of symptoms; physical examination findings; comorbidities; age of the patient; and patient preferences using both step-up and step-down approaches'. The management goals include the reduction in symptoms (e.g. congestion, itching and rhinorrhoea), physical signs of rhinitis (e.g. oedema of nasal turbinates), improvement in the patient's QoL (e.g. ability to sleep and ability to function effectively at work or school or while driving), as well as improvement in concomitant conditions (e.g. asthma). Achieving these goals requires cooperative management of exacerbations and complications by optimal use of environmental avoidance measures and tapering of medications to reduce the risk of adverse reactions. Although the guidelines recommend grading systems for control of nasal symptoms (Figure 1a) and QoL (Figure 1b), they do not, however, recommend any grading systems for ocular symptoms of AR/C.

Definition based on the Rhinitis Control Assessment Test (RCAT). The Rhinitis Control Assessment Test (RCAT), a 6-item instrument (including frequency of nasal congestion, frequency of sneezing, frequency of watery eyes, sleep interference, activity avoidance and self-assessed control), has been shown to be useful in assessing control of AR [61]. Administration of RCAT to 410 AR patients (210 with PAR and 200 with SAR; mean age 37 years and range 12–75 years) demonstrated that mean RCAT scale scores differed significantly across the groups of patients differing in

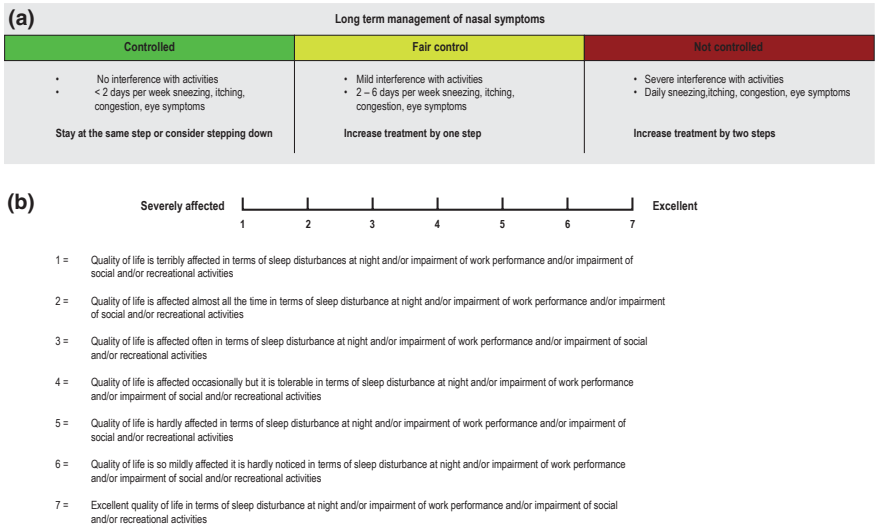

Figure 1. Classification of control of nasal symptoms (A) and QoL (B) in patients with rhinitis and allergic conjunctivitis (adapted from Wallace et al. 2008; ref [56])

physician-rated disease severity, severity reflected by total nasal symptoms scores (TNSS), physician-recommended change in therapy and physician-rated rhinitis control.

Although the RCAT does assess AR control to a certain degree, based on the summary judgment of experienced specialists who are aware of all relevant aspects of their patient's clinical status, the reliability, validity and cut-off point determination for well-controlled versus not well-controlled rhinitis need to be confirmed in further well-controlled studies of AR patients not currently being seen by a specialist. Moreover, presently the RCAT does not appear to adequately address the impact of AR on QoL or productivity/indirect costs, and thus, it is possible that modification of the RCAT to encompass these aspects of disease may provide a more robust instrument for assessment on AR control. Furthermore, the availability of a validated version of RCAT in several languages should add to the usefulness of this instrument in the assessment of AR control.

The Control of Allergic Rhinitis and Asthma Test (CARAT) [62] is a self-administered 10-item questionnaire (with items addressing nasal symptoms, 3 addressing lower airways symptoms and 1 each addressing activities, sleep impairment and treatment) recently developed for measuring control of both AR and asthma in patients with comorbid disease as recommended by the ARIA guidelines [6]. Unlike the RCAT, none of the items directly address 'control', and although the instrument has been shown to have high internal consistency and good construct validity, its usefulness needs to be confirmed in large well-controlled clinical trials and observation studies.

Definition based on total nasal/ocular symptoms scores (TNSS/TOSS) in clinical trials. It is generally assumed that to be eligible for entry to a clinical trial investigating patients with rhinitis, a patient should normally have uncontrolled rhinitis, as indicated by predetermined reflective(r) TNNS (for nasal itching, sneezing, congestion and rhinorrhoea) and rTOSS (for ocular itching/burning, tearing/watering and redness). In this setting, it can be assumed that following treatment, a total score below the predetermined value indicates a particular level of control of the symptoms of AR relative to the predetermined scores, particularly as patients grade their own symptoms and severity of symptoms before and after treatment. In addition to assessment of the conventional total and individual nasal and ocular symptoms of rhinitis [57], there is some evidence that assessment of other non-conventional outcomes such as change in colour, mucosal swelling, nasal wetness, nasal crease, sniffing, post-nasal drip, impaired sense of smell, mouth breathing, sniffles and itchy throat, rhinoconjunctivitis symptom-medication scores and nasal reactivity by nasal provocation [66–69], may also be useful in determining AR control. Indeed, one study demonstrated that statistical ranking identified the most important symptoms and signs, even though some of these were not included in the original selection criteria for defining the disease cohort, i.e. sniffing, post-nasal drip, oedematous nasal mucosa, impaired sense of smell, mouth breathing, itchy nose and many of the specific provocation factors [69].

Definition based on QoL. Assessment of QoL scores is equally useful in the assessment of control of AR. In

this regard, several validated, reproducible and relatively quick and easy to administer general-health status and disease-specific QOL instruments, particularly SF-36 [69, 70], Rhinitis Symptom Utility Index (RSUI) [71, 72] and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [1, 73–76], are commonly employed for this purpose. In the RQLQ nasal symptoms and non-hayfever symptom, domains of the instrument and the overall score were comparable in their responsiveness to the daily diary [76]. Furthermore, it appears that there is a correlation between RQLQ scores and visual analogue scales (VAS) for symptom severity [7].

Although these instruments appear to be beneficial to patients and clinicians alike, none of them specifically assess AR control, in a similar manner to the Asthma Control Test (ACT) [77], which has additionally shown to be useful in predicting future risk of asthma exacerbations in clinical trials and clinical practice [78].

Definition based on productivity. Evidence suggests that there is a link between the health of an individual and on-the-job productivity (presenteeism) and that for some chronic conditions the costs of lost productivity exceed the costs of medical care [79]. Indeed, a systematic review of studies investigating the association between presenteeism and health risks and health conditions ranging from exercise and weight to allergies and irritable bowel syndrome indicated that allergies, in particular, were associated with presenteeism [79]. In one recent study, Lamb and colleagues [80], employed the Work Productivity Short Inventory (WPSI) to assess the impact of a predefined group of health conditions on workplace productivity for the previous 12 months, by recording both absenteeism and presenteeism (lost productivity while at work) in 8267 employees at 47 employer locations in the United States. The authors demonstrated that AR was the most prevalent of the selected conditions, with 55% of the employees experiencing AR symptoms for an average of 52.5 days, being absent for 3.6 days per year due to the condition and being unproductive for 2.3 h per workday. Moreover, the mean total productivity loss per employee per year of 593 US dollars was highest for AR.

Thus, it would be reasonable to assume that AR was relatively well controlled if during the previous week it did not cause the patients to miss work and or affect their productivity, or in case of students it did not lead to significant impairment in learning and cognitive function.

Discussion

This review has clearly outlined the evidence that the symptoms of AR/C markedly impair the QoL of AR patients by adversely impacting the patients' sleep, daily activities, physical and mental status and social functioning, irrespective of the patients' geographical disposition. Moreover, AR/C adversely impacts the economic status of both the affected individual and society alike by way of decreased productivity and increased healthcare costs. Although the goal of treatment has traditionally been aimed at reducing the symptoms of AR, current thinking suggests that management should be far reaching and aimed at achieving 'overall' control of the disease, encompassing reduction in both nasal and ocular symptoms, improvement in the patient's QoL (particularly, sleep disturbance and work/school-related activity and functioning), improvement in comorbid conditions (particularly, asthma, nasal polyps, sinusitis and otitis media with effusion), as well as improving cognition (particularly as the patient's satisfaction and perceived control of disease influences their ability to deal with their disease). In view of the later, it is important that control should be scored objectively, particularly as many patients prefer not to take any pharmacotherapy and accept the symptoms of rhinitis as being a normal part of their lives, whereas other patients are constantly searching for the ideal treatment that 'works'.

There are some instruments currently available to measure control of AR, but none of these were designed to assess all aspects of the disease in a holistic manner, as described above. Moreover, a general limitation of assessing AR control is that presently there is no universally accepted and validated definition of what constitutes total AR control, thus making it difficult to set threshold limits above and below which the degree of control can be classified. Several non-traditional outcome measures, such as colour change, mucosal swelling, nasal wetness, nasal crease, sniffing, post-nasal drip, oedematous nasal mucosa, impaired sense of smell, mouth breathing, sniffles and itchy throat and rhinoconjunctivitis symptom-medication scores, which have been documented in studies investigating the effect of therapy in AR/C patients, need to be considered in addition to the traditional outcome measures currently employed. Finally, in view of a large number of patients with AR having concomitant asthma, the asthma element also needs to be considered, when formulating a definition for AR control.

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