

# Quality of life in adults and children with allergic rhinitis

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Quality of life, when referring to an individual's health, is called health-related quality of life (HRQL). HRQL focuses on patients' perceptions of their disease and measures impairments that have significant impact on the patient. Similar symptoms may vary in their effect on different individuals; the goal of therapy should be to reduce impairments that patients consider important. HRQL can be measured with generic or specific questionnaires. Specific questionnaires may be more sensitive and are much more likely to detect clinically important changes in patients' impairments. Specific questionnaires used to assess HRQL in rhinitis are the Rhinoconjunctivitis Quality of Life Questionnaire, the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire, and the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire. HRQL issues in adult rhinitis patients include fatigue, decrease in energy, general health perception, and social function; impairment of HRQL generally increases with increasing degree of symptoms and severity of disease. In children, HRQL issues include learning impairment, inability to integrate with peers, anxiety, and family dysfunction. Comorbid disorders often associated with rhinitis, including sinusitis, otitis media, and frequent respiratory infections, can further compromise HRQL. Pharmacologic treatments can have both positive and negative effects on HRQL. Agents that have troublesome adverse effects such as sedation can have a negative impact, whereas nonsedating antihistamines and intranasal corticosteroids can significantly improve HRQL in patients of all ages with rhinitis. (*J Allergy Clin Immunol* 2001;108:S45-53)

**Key words:** Allergic rhinitis, antihistamines, corticosteroids, HRQL, quality of life

Unlike many other disorders whose treatment may be centered on preventing death or future morbidity, the goal of treatment of allergic rhinitis (AR) is to improve a patient's well-being, or quality of life.<sup>1</sup> However, until recently, the treatment of AR has concentrated on symptom improvement without much focus on how this affected patient well-being. Since the 1990s, there has been an increasing trend toward assessing the impact of AR on the quality of life (QOL) of individuals with AR. It is now recognized that AR frequently has a significant impact on QOL, and as a result, QOL evaluations are often included in clinical trials.<sup>1</sup>

AR in adults and children has been shown to lead to substantial impairment of QOL, but until the past few years, this burden of disease has not been well understood. Recent clinical studies have focused on this, including the issues of impact of rhinitis on sleep, work and school performance, social relationships, and family functioning. They have also shown that a variety of pharmaceutical agents may significantly improve the QOL of affected individuals.

The term "quality of life" has various meanings, which encompass factors such as financial security, spiritual contentment, health, and the ways these factors interrelate. The component of overall QOL that pertains to an individual's health is called health-related quality of life (HRQL). This may be defined as the functional effects of an illness and its consequent therapy as perceived by the patient. It is important to appreciate that unlike conventional objective clinical measures, this definition focuses on patients' perceptions of their disease and measures the impairments that patients consider important.<sup>2</sup> In addition, it is important to appreciate that a similar level of symptom severity may have a different impact on HRQL in different patients because individuals vary in their tolerance levels. Certain individuals may be significantly bothered by mild AR symptoms, whereas a greater level of nasal symptoms may cause less HRQL impairment in others.<sup>2,3</sup> Thus therapeutic goals should be aimed at reducing impairments that the patient considers important.<sup>4</sup>

## MEASURING HEALTH-RELATED QUALITY OF LIFE

Because so many factors are involved in HRQL, there are multiple ways in which it can be measured. A variety of validated and standardized questionnaires have been developed to evaluate HRQL, including assessments of school performance, work performance, productivity,

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*Abbreviations used*

|              |                                                                          |
|--------------|--------------------------------------------------------------------------|
| AR:          | Allergic rhinitis                                                        |
| ARQLQ:       | Adolescent Rhinoconjunctivitis Quality of Life Questionnaire             |
| HRQL:        | Health-related quality of life                                           |
| MID:         | Minimal important difference                                             |
| PAR:         | Perennial allergic rhinitis                                              |
| PRQLQ:       | Pediatric Rhinoconjunctivitis Quality of Life Questionnaire              |
| PAR-ENT-QOL: | Parent Quality of Life Questionnaire                                     |
| QOL:         | Quality of life                                                          |
| RQLQ:        | Rhinoconjunctivitis Quality of Life Questionnaire                        |
| SAR:         | Seasonal allergic rhinitis                                               |
| SF-36:       | SF-36 health survey                                                      |
| WPAI-AS:     | Work Productivity and Activity Impairment-Allergy Specific Questionnaire |

and other less-formalized parameters that quantify the impact of rhinitis and its treatment on QOL.

### Health profile questionnaires

HRQL questionnaires can be classified as either generic or specific. Generic health profile questionnaires are applicable to all individuals and allow comparison of the burden of illness across different medical conditions. They can be used for any health condition and may evaluate an entire population's well-being.<sup>5</sup> The Medical Outcomes Study Short-Form Health Survey (SF-36) is a widely used and validated generic profile. It consists of 36 items that assess 3 major health attributes: functional status, well-being, and overall evaluation of health. It has been used to study a variety of medical conditions, including AR.<sup>5,6</sup> Because generic profiles must be broad and comprehensive, they may lack the detail to be responsive to small but significant changes in patients' HRQL. As a result, generic instruments are generally thought to be of limited use in focused clinical trials and clinical practice.<sup>7</sup>

Specific questionnaires are designed to evaluate a particular group of patients (eg, children), a particular function, or a particular disease and may be more sensitive because they incorporate issues that are relevant only to certain disorders. Developing disease-specific instruments involves questioning patients concerning the burdens of an illness that are most important to them. This process results in the generation of tools that closely focus on impairments that are potential targets for intervention. Disease-specific instruments are much more likely than generic questionnaires to detect clinically important changes in patients' impairments.<sup>8</sup>

Specific health-profile questionnaires designed to evaluate the HRQL in AR include the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and its age-specific adaptations—the Adolescent RQLQ (ARQLQ) for patients 12 to 17 years of age and the Pediatric RQLQ (PRQLQ) for patients 6 to 12 years of age—and the rhinosinusitis disability index.<sup>8-11</sup> In addition, the Parent QOL (PAR-ENT-QOL) Questionnaire has been devel-

oped to measure the QOL of parents whose children have otolaryngologic disorders (Table I).<sup>12</sup>

The RQLQ is one of the most widely used rhinitis-specific questionnaires. It covers 7 dimensions of health: sleep, nonnasal symptoms, practical problems, nasal symptoms, ocular symptoms, specific activities limited by symptoms in the previous week, and emotional function. Patients rate each item on a scale of 0 (not troubled) to 6 (extremely troubled). The mean value for each health dimension is calculated, and the overall HRQL is expressed as the mean of the 7 dimension scores.<sup>10</sup>

Adaptations of the RQLQ for use with adolescents and children with AR have revealed that different aspects of HRQL have varying levels of importance for adults, adolescents, and children. For example, several items related to sleep disturbance warranted inclusion of a separate sleep domain on the adult questionnaire, whereas for adolescents, only one sleep-related item was deemed important. In addition, adolescents report that AR results in problems with schoolwork and that they are troubled by generally not feeling well.<sup>9</sup>

The PRQLQ has 23 items in 5 domains (nasal symptoms, ocular symptoms, other symptoms, practical problems, and activities) that children answer on the basis of the previous week. Validation of the instrument has shown that most children give reliable and accurate responses (although some younger children have difficulty understanding the concept of "during the last week") and that the PRQLQ is appropriate for clinical trials, clinical practice, and surveys.<sup>8</sup> According to the PRQLQ, children, adults, and adolescents are bothered by the physical symptoms of AR to a similar degree, but children are not as bothered by emotional problems or limitations of activities.

Another AR-specific questionnaire is the rhinosinusitis disability index. This measures the self-perceived impact of otolaryngologic disorders and has been validated for use in patients with AR or sinus disease.<sup>11</sup> The PAR-ENT-QOL questionnaire has been developed to assess the impact of children's recurrent otolaryngologic infections on their parents' QOL. This questionnaire focuses primarily on the consequences of otolaryngologic disorders on family life.<sup>12</sup> Few standardized questionnaires exist that specifically examine work or school performance. Nonetheless, these issues are also important parameters for study because reduced performance may lead to a compromise of future opportunities.

### Utilities

Utilities are used to measure the value of health states, as determined by either the patient or society. They provide a single number denoting an individual's QOL. The Standard Gamble and the Time Trade-Off are generic utilities that establish the value an individual places on his or her own health.<sup>13</sup> Other utilities such as the Quality of Well-Being Scale and the Multiattribute Health Utilities Index determine societies' value of different health states.<sup>14,15</sup> When first introduced, utility instruments were only generic forms, limiting their respon-

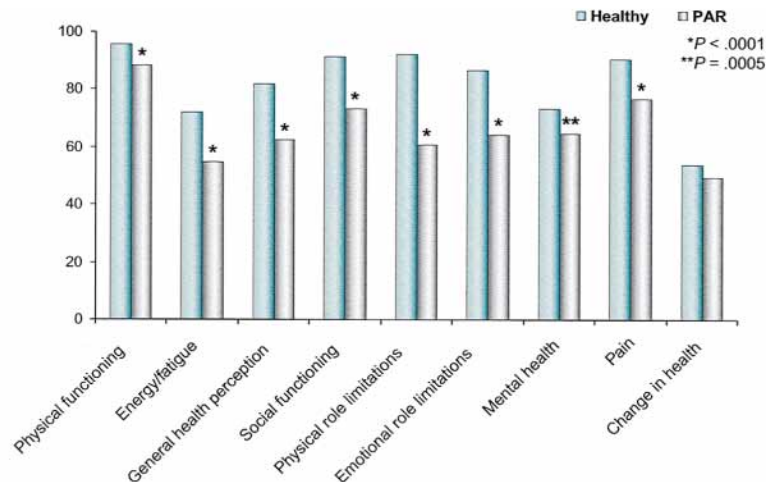


**FIG 1.** QOL scores in adults with PAR and healthy control subjects. (Data from Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol* 1994;94:182-8.)

**TABLE I.** HRQL questionnaires used for AR

| Instrument                                                           | Type             | Patients |
|----------------------------------------------------------------------|------------------|----------|
| SF-36 Health Survey                                                  | Generic          | Adults   |
| Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)             | Disease-specific | Adults   |
| Rhinitis Quality of Life Questionnaire                               | Disease-specific | Adults   |
| Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) | Disease-specific | 12–17 y  |
| Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)* | Disease-specific | 6–12 y   |
| Rhinosinusitis Disability Index                                      | Disease-specific | Adults   |
| PAR-ENT Quality of Life Questionnaire                                | Disease-specific | Adults   |

From Juniper EF. Quality of life in adults and children with asthma and rhinitis. *Allergy* 1997;52:971-7. © 1997 Munksgaard International Publishers Ltd. Copenhagen, Denmark.

\*The full text of this questionnaire is published in Reference 9.

siveness to small but significant changes in patient status. Recent adaptations of some utility instruments improved their measurement properties as disease-specific instruments for adults with AR and children with asthma.<sup>16,17</sup>

### Clinical relevance of HRQL measurements

Unlike many clinical variables that are relatively simple to quantify and evaluate, changes in HRQL scores are often hard to interpret because these scores are based on arbitrary scales and are not associated with any units. To overcome these problems, Juniper et al<sup>1,18</sup> developed the concept of the “minimal important difference” (MID) to help clinicians interpret HRQL data in a meaningful context. The MID is the smallest difference in the degree of clinical improvement that would justify a change in the patient’s treatment in the absence of troublesome side effects or excessive cost. For example, a change in score on the RQLQ of greater than approximately 0.5 represents the MID for this tool.<sup>19</sup> Changes in scores of 1.0 represent moderate changes, and differences of 1.5 are indicative of large changes in patients’ perceived HRQL.

### IMPACT OF AR ON HRQL Adults with AR

The first studies that documented the impact of AR on HRQL were conducted in adults. In one study describing HRQL impairment caused by AR, 111 patients with moderate to severe perennial AR (PAR) and 116 healthy volunteers were administered the SF-36 Health Survey to assess HRQL. Significant decreases in physical functioning, energy/fatigue, general health perception, social functioning, physical and emotional role limitations, emotions, mental health, and pain were noted in those with PAR compared with control subjects (Fig 1).<sup>5</sup> This study demonstrated that PAR-associated HRQL impairment is significant enough to be detected on a generic HRQL instrument. In fact, this study found PAR to impair HRQL to a degree similar to that seen in patients with asthma, which has long been recognized to have a significant impact on QOL.<sup>20</sup>

A US nationwide survey of 15,000 households conducted to determine the prevalence and impact of AR

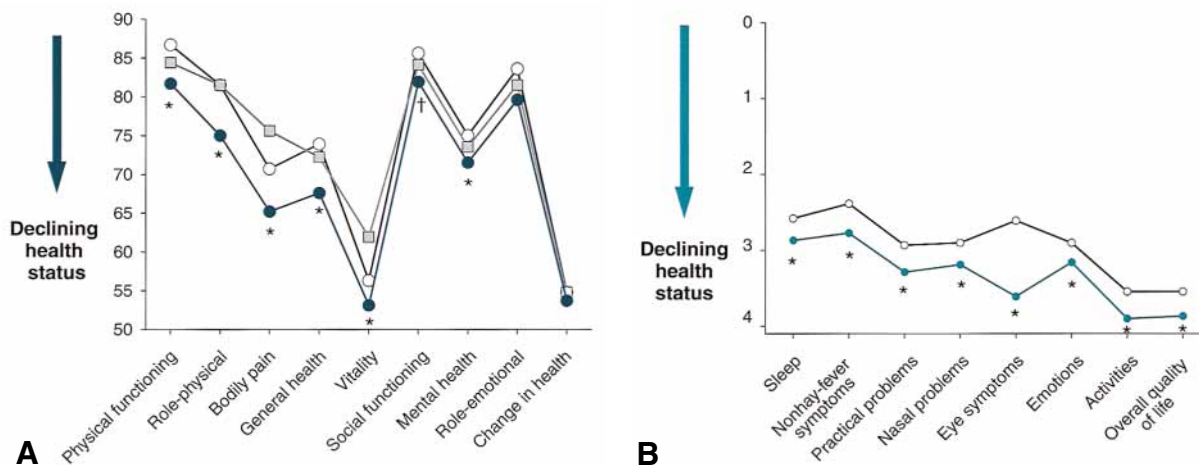


**FIG 2. A,** Impact of nasal/ocular symptoms on HRQL as measured by the SF-36 and RQLQ. SF-36 health profiles of patients with nasal/ocular symptoms (black circles;  $n = 312$ ) vs healthy control subjects (white circles;  $n = 139$ ). Parameters on far left measure physical health; parameters on far right measure mental health; intermediate parameters measure both. Lower score indicates poorer health status. Squares indicate mean values ( $n = 2474$ ). \* $P < .01$  vs control; † $P < .05$  vs control. **B,** Impact of nasal/ocular symptoms on HRQL as measured by SF-36 and RQLQ. RQLQ health profiles of patients with nasal/ocular symptoms (black circles;  $n = 312$ ) vs healthy control subjects (white circles;  $n = 965$ ). Higher score indicates poorer health status. \* $P < .01$  vs control. (A and B from Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99:S805-28. With permission.)

demonstrated that AR results in significant reductions in HRQL as measured by both the SF-36 and the RQLQ. In this study, a subset of 312 individuals with nasal and ocular symptoms completed both the SF-36 questionnaire and the RQLQ. The responses of these individuals were compared with those of healthy control subjects. Analysis revealed statistically significant differences in all dimensions of the RQLQ and 7 of 9 dimensions of the SF-36 (Fig 2). Individuals experiencing at least 31 days of rhinitis symptoms in a year noted significant impairment in HRQL, particularly with respect to their ability to perform normal physical roles. Repeated nose blowing, disrupted sleep patterns, and inability to concentrate were among the characteristics that contributed to considerable impairment of HRQL.<sup>6</sup>

To assess the correlation of daily AR symptom severity and nasal hyperreactivity with QOL, de Graaf-in't Veld et al<sup>3</sup> assessed 48 adults with PAR. Patients recorded nasal symptoms in diaries over a 2-week period, answered the RQLQ, and underwent a histamine challenge test to assess for nasal hyperreactivity. Scores for the overall and individual QOL domains of the RQLQ were moderately but statistically significantly correlated with total nasal symptoms, with the degree of HRQL impairment increasing with the degree of symptoms. However, individual QOL domains and individual symptoms were not equally correlated. Some patients might be impaired by only a few nasal symptoms, whereas others might be less impaired by the same symptoms or more severe symptoms. Therefore, QOL assessments and symptom scores are not necessarily measuring the same parameters. In addition, nasal hyperreactivity scores were significantly correlated with total and individual

symptoms and overall HRQL and individual domains except sleep and emotions. Thus daily nasal symptoms, nasal hyperreactivity, and HRQL scores are moderately correlated in patients with PAR, indicating that generally, increased severity of AR causes increased HRQL impairment.

HRQL impairments associated with AR may also significantly impact mood and learning ability. The effects of untreated seasonal AR (SAR) on a variety of neuropsychiatric parameters in patients with AR were examined to evaluate mood and cognitive function. Allergic and control subjects were tested with respect to speed of cognitive processing, psychomotor speed, ability to sustain attention, verbal learning and memory, and mood. Only atopic subjects had significant decreases in verbal learning, decision-making speed, psychomotor speed, reaction time tests, and positive affect scores during the allergy season (Fig 3).<sup>21</sup> These results indicate that AR does have a significant impact on many aspects of cognitive function and affect.

AR symptoms have been found to impair productivity in the workplace. The Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) questionnaire has been developed and validated to measure the effect of AR on work productivity (among adults), classroom activity (among students), and regular activities. It assesses function-related end points, providing a measure of the economic impact of AR and the potential of therapeutic interventions. In a study of 422 adults with rhinitis, moderate to severe SAR symptoms were responsible for 35% to 40% impairment of normal productivity at work. However, on average, only 1.7% of work time was missed. Improvements in total symptom scores with ther-

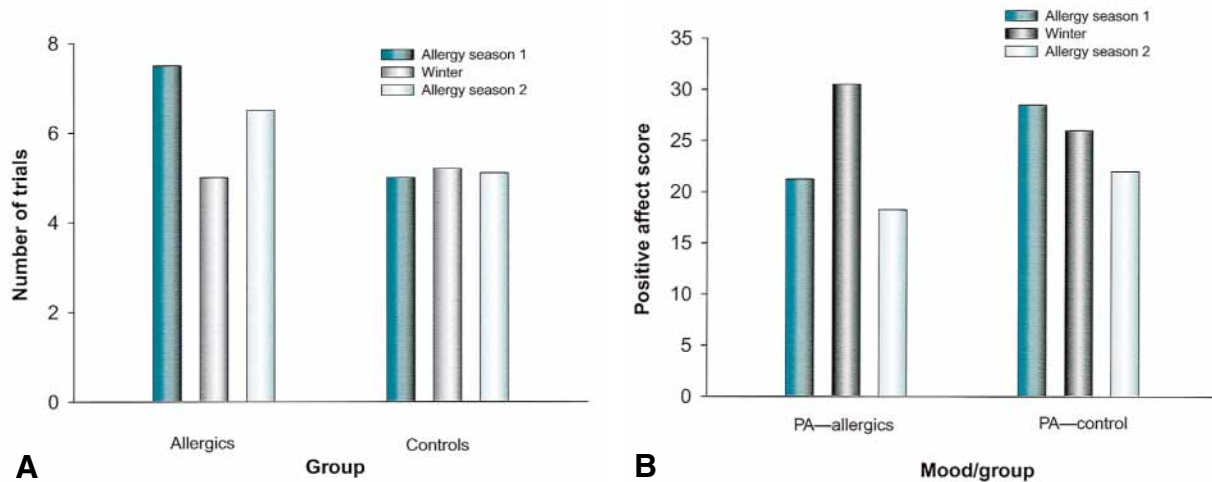


**FIG 3. A,** Effect of AR on learning and mood. Changes in mean number of trials needed to learn a list of 12 words (Buschke Selective Reminding Test) in- and out-of-allergy seasons by group. **B,** Effect of AR on learning and mood. Changes in positive affect (PA). Scores on positive-negative affect scales, in- and out-of-allergy season by group. (A and B reprinted with permission of Ann Allergy Asthma Immunol 1993;71:251-8. Copyright 1993.)

**TABLE II.** Impact of allergic rhinitis among adolescents

|                           | Rhinitis | Rhinitis-like symptoms | Asymptomatic | P value* |
|---------------------------|----------|------------------------|--------------|----------|
| Asthma                    | 28%      | 26%                    | 10%          | < .01    |
| Sleep loss                | 7%       | 8%                     | 3%           | < .01    |
| Activity limits           | 43%      | 52%                    | 27%          | < .01    |
| Lack of self-satisfaction | 12%      | 22%                    | 10%          | < .01    |

From Arrighi HM, Cook CK, Redding GJ. The prevalence and impact of allergic rhinitis among teenagers. *J Allergy Clin Immunol* 1996;97:430. With permission.

\* $\chi^2$ ; 2 degrees of freedom.

apy correlated with improvements in the degree of impairment.<sup>22</sup>

### Children with AR

AR in children results in a variety of problems that may impair HRQL. In addition to issues of a practical nature that also affect adults, such as the need to rub the eyes and nose, blow nose repeatedly, carry tissues, and take medications, children may have a variety of other limitations. For example, children may have problems at school because of a learning impairment or may be unable to participate in individual or family activities such as playing sports on grass, playing with pets, and camping trips that will probably elicit allergic symptoms. In addition, children may have emotional disturbance as a result of an inability to fully integrate with their peers and they may feel isolated, leading to frustration, sadness, and anger. These impairments can lead to behavioral problems that are not necessarily attributed to AR.<sup>4</sup> Growing evidence suggests that parents may not correctly perceive the issues affecting their children.<sup>8</sup> Chronic conditions such as PAR have been linked to a range of other effects including sleep disturbances, anxiety, school problems, and familial dysfunction.<sup>23</sup>

In a study of 2084 adolescents 13 or 14 years of age, those who had either physician-diagnosed AR or rhinitis-

like symptoms were significantly more likely to report sleep loss, activity limitations, and lack of self-satisfaction (Table II). Those who had rhinitis-like symptoms without a diagnosis (8% of the population) were more likely to report impairments than those with physician-diagnosed AR, suggesting that inadequate symptom identification and control contribute to impairment. Childhood AR may be overlooked and undertreated, particularly because younger children with rhinitis may not recognize and/or report their symptoms. This study underscores the importance of identifying these children to improve their HRQL through effective treatments.<sup>24</sup>

Children with AR may have school problems including absences and poor performance caused by distraction, fatigue, or irritability. In the United States alone, children miss approximately 2 million school days per year because of symptoms of AR.<sup>25</sup> Some school absences may be unwarranted if the child's family or school misclassifies nasal allergic symptoms as sinus or middle ear infections.<sup>23</sup> School difficulties in children are also associated with the adverse effects of medications, such as antihistamines and decongestants. These may cause drowsiness or irritability resulting in impaired school performance or behavioral problems.<sup>26</sup> Significant sleep disturbances can be caused by congestion associated with AR and some medications used to treat

the condition. Disrupted sleep patterns and sleep loss often lead to daytime fatigue and poor concentration in school, resulting in learning impairment.<sup>23,27</sup>

It is particularly important to recognize and treat AR in children to prevent school and behavioral problems associated with this disorder. It appears that many children and adolescents with AR remain undiagnosed and untreated.<sup>24</sup> Alleviating problems with school performance and behavior in childhood may help to enhance lifelong opportunities and QOL.

Children with AR may have peer and social tension as a result of their disorder. For example, symptoms such as frequent sneezing, rhinorrhea, or nose blowing may disrupt classrooms and annoy classmates. Such symptoms could readily lead to labeling by peers and embarrassment to the affected child. In addition, issues of appearance are particularly important to preteens and teenagers. Therefore, effects of inadequately treated AR on children's faces, including the "allergic crease" (a characteristic line across the nose resulting from upward rubbing), the infraorbital dark circles ("shiners"), and open mouth ("dull look") may also contribute to labeling by peers. Furthermore, the need to take medication and limitations on activities as a result of symptoms may further contribute to isolation. All of these factors may lead to diminished self esteem for affected children.<sup>23</sup>

Allergen avoidance measures aimed at improving the management of AR also affect children's HRQL. Controls may include the need to curtail activities and stay indoors to avoid pollen and mold. This reduces opportunities to interact with peers. In addition, measures to minimize exposure to dust mites, mold spores, and animal dander include removing carpets, encasing mattresses, box springs, and pillows, eliminating stuffed toys, and removing a family pet.<sup>28</sup> Clearly, children with AR, disturbed by these changes and limitations on activities and environment, may have significantly decreased HRQL.

Chronic conditions, including AR, may adversely impact the QOL of the patients' families as well. Parents may become anxious and overprotective or feel guilty and even hostile toward affected children. Siblings may be deprived of needed attention, develop their own emotional disturbances, and harbor resentment toward their brother or sister. Additional adverse effects on the family may include disruption of sleep, fatigue, work absences, ruined family holidays, interference with family social life, and draining of family resources.<sup>23</sup> Symptoms of rhinitis are particularly troublesome to parents of young children; however, they may be less aware of other related problems, such as sleep disturbances.<sup>7</sup>

### **Influence of comorbid disorders of AR on QOL**

Failure to adequately treat AR may lead to a variety of comorbid conditions including asthma, sinusitis, otitis media, frequent respiratory infections, and orthodontic malocclusions, all of which may further impair HRQL.<sup>29,30</sup> Children with multiple chronic conditions have increased morbidity across a variety of mea-

sures.<sup>31</sup> An analysis of the 1988 National Health Interview Survey on Child Health to determine the impact of multiple chronic conditions on children's health found that the most prevalent condition pairs were allergy related.<sup>31</sup> The prevalence of developmental delay, learning disabilities, and emotional and behavioral problems increased sharply with the number of chronic conditions reported. In addition, deterioration of health status measures including days in bed, school absences, and activity limitation was noted with increasing numbers of chronic conditions. These findings emphasize the need for adequate diagnosis and treatment of AR to avoid further HRQL impairment by preventing some of the development and reducing the magnitude of comorbid disorders.

### **IMPACT OF PHARMACOLOGIC TREATMENT ON QOL**

Many medical interventions, including nonsedating antihistamines, intranasal corticosteroids, and immunotherapy are approved for use in adults and children and have been shown to improve HRQL of individuals with AR. However, some treatments have been found to worsen certain assessments of HRQL due to troublesome adverse events.

#### **Treatment with first-generation sedating antihistamines**

Many first-generation sedating antihistamines, such as diphenhydramine and triprolidine, are approved for adults and for children under the age of 12 years and are available without a prescription. They are known to cross the blood-brain barrier and produce sedation, which may impair some measures of HRQL. Sedating antihistamines have been associated with decreased performance both at work and at school and have been linked to an increased incidence of automobile accidents.

Sedating antihistamines negatively impact performance by affecting sustained attention, cerebral processing, visual function, and reaction time.<sup>32</sup> An analysis of work-related injuries among employees who used sedating antihistamines found employees to be at risk of lapses and significant errors that may lead to potential hazards and decreased work productivity and to have a greater risk of sustaining an injury.<sup>33</sup> Sedating antihistamines such as triprolidine have been found to affect driving performance such that after administration, drivers exhibited weaving behavior typically observed in subjects with blood alcohol levels of 0.05%, lasting up to 4 hours.<sup>34</sup> Daytime sleepiness and decreased alertness may also result after the evening use of first-generation H<sub>1</sub> receptor antagonists.<sup>35,36</sup> Sedating antihistamines have also been shown to reduce learning performance in children.<sup>26</sup> Further compounding the increased risk for traumatic work-related injuries, poor school and work performance, and impaired driving caused by these agents, patients do not accurately recognize their level of sedation.<sup>32,37</sup>

## Treatment with second-generation nonsedating antihistamines

The second-generation nonsedating antihistamines (eg, loratadine, terfenadine, astemizole, and fexofenadine) do not usually cause sedation or performance impairment, and several are indicated for children under 12 years of age.<sup>32,37</sup> Two studies have shown them to improve classroom performance. To assess the effects of various treatments for AR on learning performance, children with SAR and healthy control subjects were instructed on the use of a didactic computer simulation in a classroom situation. Children with SAR received 25 mg diphenhydramine (a sedating antihistamine), 10 mg loratadine, or placebo, whereas healthy children were not treated. The mean composite learning score in children treated with either placebo or diphenhydramine was significantly less than that of healthy children. The composite learning score of children who received loratadine exceeded both of the other atopic groups and did not differ significantly from the healthy control subjects (Fig 4).<sup>26</sup> These results indicate that AR significantly reduces the learning ability of children and that this adverse effect may be counteracted by treatment with second-generation nonsedating H<sub>1</sub> receptor antagonists but is exacerbated by treatment with a sedating antihistamine.<sup>26</sup>

Further evidence of the ability of nonsedating antihistamines to reduce classroom impairment associated with AR comes from a study of college students. The WPAI-AS instrument was used to determine the level of classroom impairment of 241 students (mean age, 22.8 years) with AR. Rhinitis symptoms were responsible for a loss of 4.7% of regular classroom hours and were considered by the patients to impair classroom performance by 38%. After 2 weeks of therapy with fexofenadine, improvements in total symptom scores correlated with decreases in the degree of impairment.<sup>22</sup>

Studies of other nonsedating antihistamines have confirmed their benefits with regard to improvement of QOL parameters. A placebo-controlled, double-blind, randomized study of 845 adults with moderate to severe SAR examined the effect of 120 or 180 mg fexofenadine daily on HRQL and impairment at work and in daily activities. Assessment tools included the RQLQ, the WPAI-AS, and portions of the SF-36 survey. Participants answered questionnaires at baseline and after 1 and 2 weeks of therapy. Patients treated with the nonsedating antihistamine reported significantly greater improvement ( $P \leq .006$ ) in overall RQLQ than patients receiving placebo and significantly less overall work and daily activity impairment compared with the group receiving placebo ( $P \leq .004$ ).<sup>38</sup> Improvements in HRQL indexes have also been found after treatment with 60 mg fexofenadine twice daily.<sup>39</sup>

Another study compared symptoms and HRQL in 274 patients with PAR treated with the low-sedating antihistamine, 10 mg cetirizine daily, or placebo. The SF-36 health survey was administered at baseline and after 1 and 6 weeks of treatment. After 6 weeks, the percentage of days without rhinitis or with only mild rhinitis symptoms was significantly greater for the cetirizine group

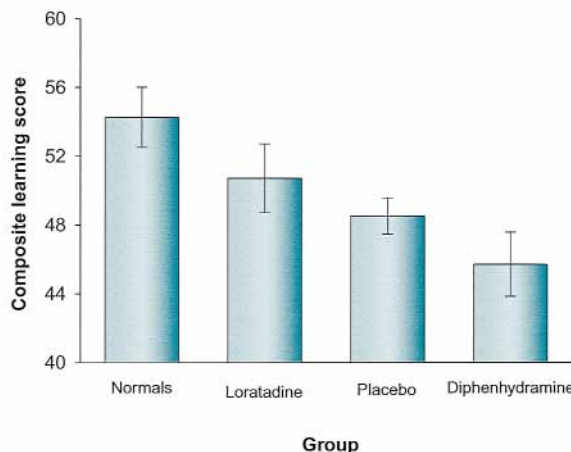


**FIG 4.** Effects of AR and antihistamines on learning. Mean ( $\pm$  standard error) composite learning score for every treatment group. (Reprinted with permission of Ann Allergy Asthma Immunol 1993;71:121-6. Copyright 1993.)

( $P < .0001$ ) compared with placebo, and significant improvement ( $P \leq .01$ ) was noted for all HRQL parameters at 1 and 6 weeks.<sup>40</sup>

The addition of a decongestant to antihistamine therapy was evaluated in a randomized trial of 193 patients with SAR and mild asthma. Patients received both 5 mg loratadine twice daily and 120 mg pseudoephedrine twice daily or placebo for 6 weeks. Nasal and pulmonary symptoms were recorded daily, and HRQL was assessed at baseline and at the conclusion of the study. Rhinitis and asthma symptom scores were significantly reduced in patients in the active treatment group compared with those who received placebo. Pulmonary function improved as well. Select QOL measures improved significantly for patients in the loratadine and pseudoephedrine group compared with those in the control group.<sup>41</sup>

## Treatment with intranasal corticosteroids

Intranasal corticosteroids have also been shown to significantly improve HRQL in adults with AR, and many of these preparations are approved for use in children. In addition to being the most potent anti-inflammatory medications available for the relief of AR, intranasal corticosteroids significantly reduce nasal blockage, making them particularly useful for patients affected by this symptom. This is important because the congestion associated with AR can predispose to nasopharyngeal collapse and airway obstruction. This may cause an increased number of sleep microarousals, and the sleep disturbance may result in daytime fatigue, reduced energy levels, impaired performance, and negative affect.

In a study of 20 patients with PAR designed to investigate the effects of intranasal corticosteroids on sleep and daytime alertness, flunisolide was found to significantly reduce congestion ( $P < .001$ ) and reduce sleep problems ( $P < .05$ ). The analysis of daytime alertness tended to favor flunisolide but did not reach significance ( $P = .08$ ).<sup>42</sup> In a separate study, intranasal fluticasone

propionate was found to significantly improve HRQL as measured by the RQLQ in adults with SAR. Patients treated with fluticasone had significantly better scores on all domains of the RQLQ after 2 weeks of treatment than those receiving placebo ( $P < .05$ ).<sup>43</sup>

The impact of intranasal corticosteroids on HRQL was assessed in 146 children with perennial rhinitis. Children received either beclomethasone dipropionate or ipratropium bromide for 6 months. HRQL questionnaires were completed at baseline and after 6 months. Both medications were effective for reducing perennial rhinitis symptoms, and both significantly improved QOL assessments. Measures documented interference with sleep, daily activities, concentration in school, and disturbance of mood were significantly improved ( $P < .05$ ).<sup>44</sup>

### Treatment with immunotherapy

AR may be treated by immunotherapy, also known as hyposensitization, when the degree of symptoms is unacceptable and avoidance measures and pharmacotherapy either produce unacceptable side effects or fail to sufficiently control symptoms.<sup>45</sup> This treatment has also been shown to improve HRQL. Sixty adult patients who received at least 1 year of quantified testing-based immunotherapy were evaluated with a QOL questionnaire and individual interviews to determine changes in physical, social, and emotional well-being and productivity. The majority of the patients who received immunotherapy noted a significant improvement in all areas within 4 to 6 months of the initiation of immunotherapy. Despite the time-consuming nature and additional expense of immunotherapy, 92% of the participants believed that this therapy was worthwhile.<sup>46</sup> The use of immunotherapy for children with AR is also valuable but may be limited by the necessity for frequent injections and the small risk of anaphylactic reactions.<sup>45</sup>

### CONCLUSIONS

Symptoms of AR can markedly interfere with HRQL and may predispose adults and children to a variety of comorbid conditions, which may further affect HRQL. The development and validation of a number of health profile tools has allowed investigators to document the significant impairment of QOL experienced by adults and children with AR. Inclusion of HRQL parameters in clinical trials has shown that effective therapy of AR with non-sedating antihistamines, intranasal corticosteroids, and other common approved treatments results in improvements on HRQL questionnaires. Physicians should take into account the impact of AR on HRQL and consider treatment interventions that provide safe and efficacious ways to minimize the impact of this disease. Better diagnosis and treatment can help to greatly benefit patients affected by AR.

### REFERENCES

1. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47:81-7.
2. Juniper EF. Measuring health-related quality of life in rhinitis. *J Allergy Clin Immunol* 1997;99:S742-9.
3. de Graaf-in't Veld T, Koenders S, Garrelds IM, Gerth van Wijk R. The relationships between nasal hyperreactivity, quality of life, and nasal symptoms in patients with perennial allergic rhinitis. *J Allergy Clin Immunol* 1996;98:508-13.
4. Baraniuk JN, Meltzer EO, Spector SL. Impact of allergic rhinitis and related airway disorders. *J Respir Dis* 1996;17:S11-23.
5. Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol* 1994;94:182-8.
6. Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99:S805-28.
7. Juniper EF. Quality of life in adults and children with asthma and rhinitis. *Allergy* 1997;52:971-7.
8. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol* 1998;101:163-70.
9. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol* 1994;93:413-23.
10. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77-83.
11. Benninger MS, Senior BA. The development of the Rhinosinusitis Disability Index. *Arch Otolaryngol Head Neck Surg* 1997;123:1175-9.
12. Berdeux G, Hervie C, Smajda C, Marquis P. Parental quality of life and recurrent ENT infections in their children: development of a questionnaire: Rhinitis Survey Group. *Qual Life Res* 1998;7:501-12.
13. van Wijk EE, Bosch JL, Hunink MG. Time-tradeoff values and standard-gamble utilities assessed during telephone interviews versus face-to-face interviews. *Med Decis Making* 1998;18:400-5.
14. Kaplan RM, Anderson JP, Wu AW, Mathews WC, Kozin F, Orenstein D. The Quality of Well-being Scale: applications in AIDS, cystic fibrosis, and arthritis. *Med Care* 1989;27:S27-43.
15. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system: Health Utilities Index Mark 2. *Med Care* 1996;34:702-22.
16. Revicki DA, Leidy NK, Brennan-Diemer F, Thompson C, Togias A. Development and preliminary validation of the multiattribute Rhinitis Symptom Utility Index. *Qual Life Res* 1998;7:693-702.
17. Torrance GW. Measurement of health state utilities for economic appraisal. *J Health Econ* 1986;5:1-30.
18. Juniper E. Health-related quality of life in rhinitis. In: RM Naclerio SD, N Mygind, editors. *Rhinitis mechanisms and management*. New York: Marcel Dekker, Inc; 1999. p. 135-46.
19. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996;98:843-5.
20. Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE Jr, et al. Quality of life in asthma. I: internal consistency and validity of the SF-36 questionnaire. *Am J Respir Crit Care Med* 1994;149:371-5.
21. Marshall PS, Colon EA. Effects of allergy season on mood and cognitive function. *Ann Allergy* 1993;71:251-8.
22. Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. *Clin Drug Invest* 1996;11:278-88.
23. Richards W. Preventing behavior problems in asthma and allergies. *Clin Pediatr (Phila)* 1994;33:617-24.
24. Arrighi HM, Cook CK, Redding GJ. The prevalence and impact of allergic rhinitis among teenagers. *J Allergy Clin Immunol* 1996;97:430.
25. Meltzer EO. Antihistamine- and decongestant-induced performance decrements. *J Occup Med* 1990;32:327-34.
26. 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.
27. Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* 1996;17:185-9.
28. Dykewicz MS, Fineman S, Nicklas R, Lee R, Blessing-Moore J, Li JT, et al. Joint Task Force algorithm and annotations for diagnosis and management of rhinitis. *Ann Allergy Asthma Immunol* 1998;81:469-73.

29. Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol* 1997;99:S773-80.
30. Passali D, Mösges R, Hassan HA, Bellusi L, Working Group. International Conference on Allergic Rhinitis in Childhood. *Allergy* 1999;54:S7-34.
31. Newacheck PW, Stoddard JJ. Prevalence and impact of multiple childhood chronic illnesses. *J Pediatr* 1994;124:40-8.
32. Nolen TM. Sedative effects of antihistamines: safety, performance, learning, and quality of life. *Clin Ther* 1997;19:39-55; discussion 32-3.
33. Gilmore TM, Alexander BH, Mueller BA, Rivara FP. Occupational injuries and medication use. *Am J Ind Med* 1996;30:234-9.
34. Meltzer EO. Performance effects of antihistamines. *J Allergy Clin Immunol* 1990;86:613-9.
35. Goetz DW, Jacobson JM, Apaliski SJ, Repperger DW, Martin ME. Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine. *Ann Allergy* 1991;67:448-54.
36. Kay GG, Berman B, Mockoviak SH, Morris CE, Reeves D, Starbuck V, et al. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch Intern Med* 1997;157:2350-6.
37. Kay GG, Plotkin KE, Quig MB, Starbuck VN, Yasuda S. Sedating effects of AM/PM antihistamine dosing with evening chlorpheniramine and morning terfenadine. *Am J Managed Care* 1997;3:1843-8.
38. Meltzer EO, Casale TB, Nathan RA, Thompson AK. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1999;83:311-7.
39. Tanner LA, Reilly MA, Meltzer EO, Bradford JE, Mason J. Evaluation of quality of life and health economic measures in patients treated with fexofenadine HCl for seasonal allergic rhinitis [abstract]. *Ann Allergy Asthma Immunol* 1997;78:125.
40. Bousquet J, Duchateau J, Pignat JC, Fayol C, Marquis P, Mariz S, et al. Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire. *J Allergy Clin Immunol* 1996;98:309-16.
41. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma [published erratum appears in *J Allergy Clin Immunol* 1998;101(6 Pt 1):792]. *J Allergy Clin Immunol* 1997;100:781-8.
42. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. *J Allergy Clin Immunol* 1998;101:633-7.
43. Ratner PH, van Bavel JH, Martin BG, Hampel FC Jr, Howland WC III, Rogenes PR, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract* 1998;47:118-25.
44. Milgrom H, Biondi R, Georgitis JW, Meltzer EO, Munk ZM, Drda K, et al. Comparison of ipratropium bromide 0.03% with beclomethasone dipropionate in the treatment of perennial rhinitis in children [In Process Citation]. *Ann Allergy Asthma Immunol* 1999;83:105-11.
45. Meltzer EO. Treatment options for the child with allergic rhinitis. *Clin Pediatr (Phila)* 1998;37:1-10.
46. Fell WR, Mabry RL, Mabry CS. Quality of life analysis of patients undergoing immunotherapy for allergic rhinitis. *Ear Nose Throat J* 1997;76:528-36.