Sleep is fundamental for physical and mental health as well as daytime performance and represents a crucial aspect in the personal representations of well-being. Sleep disturbances in patients with chronic disorders contribute to exacerbate symptoms, complicate management, and affect mood and quality of life (QoL). Allergic diseases are a global health problem of increasing prevalence that affects up to 15% of the population in Western countries. Sleep problems associated with allergic diseases may play a role in worsening the burden of illness, contributing to impairment of the QoL.

The aim of this review was to describe the most common causes leading to sleep disturbance in allergic patients and their consequences on the QoL. The possible negative effects of treatment on sleep parameters has been also considered.

Allergic diseases constitute a global health problem of increasing prevalence that has been labeled as the epidemic of the 21st century. They affect up to 15% of the population in Western countries and have a substantial burden not only on medical costs and socioeconomic outcomes, but also on subjective well-being and daily functioning. The recent literature on the quality of life (QoL) provide a clear picture about allergy in real terms, showing that allergic patients experience physical, emotional and practical problems, and have limitations in social life, work and leisure activities.

Sleep, in which people spend approximately a third of their life, is essential for physical and mental health as well as daytime performance and in other words constitutes a crucial aspect in the personal representations of well-being. Literature data clearly indicate how the presence of sleep disturbances in patients with chronic disorders may exacerbate symptoms, complicate management, and affect mood as well as the QoL.

Sleep problems associated with allergic diseases constitute a troublesome factor that exacerbates the burden of illness, contributing to impairment of the QoL.

The aim of this review was to describe the most common causes leading to sleep disturbance in allergic patients and their consequences on QoL. A literature search in the database MEDLINE was performed using the following keywords separately and in combination: allergy, asthma, atopic dermatitis, urticaria, sleep, sleep disturbance, insomnia, daytime sleepiness.

Sleep Disturbances

Sleep disturbances can be defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). They are classified as dyssomnias (characterized by abnormal behavioral or physiological events occurring in association with sleep, specific sleep stages, or sleep–wake transitions). Sleep disorders can be either primary or secondary to mental disorders, somatic disorders or be substance induced (Fig. 1).

The prevalence of sleep disturbances is high: approximately 35% of adults experience transient or occasional difficulties sleeping, and 10–20% suffer from chronic sleep disturbances. This is probably an underestimate: due to individual adaptation and adjustment processes, many patients do not report their sleep problems to healthcare professionals. Although poor sleep is often accepted as ‘the norm’, it has a detrimental impact on daily functioning and QoL even in healthy people.

Sleep disturbances express themselves in daily life, making people more susceptible to cognitive impairment (memory, learning abilities, concentration), functional problems (impaired psychomotor function and procedural skills, decrease productivity, increased accidents) and psychological consequences (fatigue, irritability, malaise, anxiety, depression). The effects in terms of costs to society are also considerable. An association between subjective complaints of daytime sleepiness, inadequate sleep time, insomnia and an indirect measure of healthcare utilization has been demonstrated in a community-based study, involving more than 6400 participants.

Allergic Diseases and Sleep Disturbances

The causes of sleep disturbances in allergic diseases are numerous and also include those factors that are important to the general population, such as insufficient or ineffective sleep, circadian rhythm disturbance and inadequate sleep hygiene. Nevertheless, evidence suggests that allergy itself can disrupt sleep: the presence of troublesome symptoms, difficulty in obtaining optimal disease control, and contributing psychological reactions of a chronic condition (irritability, anxiety, depression) trigger a vicious circle in which allergy interferes with sleep, and sleep has significant relapses on QoL related to the disease. Besides, the disease impact of sleep has been emphasized by the international guidelines for respiratory allergy. In fact both the Global Initiative for Asthma (GINA) and Allergic Rhinitis and its Impact on Asthma (ARIA) documents have introduced the presence of disrupted sleep as a component in providing a classification of the disease.

A further aspect in the management of allergic diseases is that anti-allergic drugs can alter sleep due to their effect on the central nervous system.

In particular, insomnia and sleep-disordered breathing were found to be the most common causes for sleep disturbances in the articles reviewed. Insomnia can be considered...
as ‘a perception by the patient that his sleep is inadequate or abnormal’. The DSM-IV defines insomnia as a persistent complaint of difficulty initiating sleep, difficulty maintaining sleep and nonrestorative sleep. These difficulties should cause daytime sleepiness with decreased daily functioning. Insomnia is defined as primary (when the sleep difficulties are not related with mental disorders, somatic disorders or substance use) and secondary (when it is associated with the above described causes).9

The term ‘sleep-disordered breathing’ describes a large spectrum of abnormal respiration during sleep, ranging from primary snoring to obstructive sleep apnea (OSA) (Figs 2 and 3). Snoring occurs in at least 20% of the population and 50% of men over 50 snore. Most snorers are ‘simple’ or ‘nonapneic’, as the prevalence of snoring is much higher than that of sleep apnea.21,25,26

**Assessment of Sleep Disturbance**

Both generic and specific tools are available for the assessment of the subjective impact of sleep disturbances on the QoL and some of these have been used in allergic disorders (Table 1). The Sickness Impact Profile (SIP)27 and the Nottingham Health Profile (NHP),28 two widely used health status measures, include a sub-scale specifically addressed to sleep. A 12-item index that evaluates sleep problems has also been validated in the context of the Medical Outcome Study29 in different chronic diseases. It measures six concepts related to sleep quality: sleep initiation, maintenance, respiration, adequacy, somnolence and quantity.

The Epworth Sleepiness Scale (ESS)30 is a simple, self-administered questionnaire measuring the risk of falling asleep different specific situations that are commonly met. It consists of eight questions asking the respondent to rate the potential for falling asleep in sedentary situations on a 4-point Likert scale from 0 (never) to 3 (high chance). The total of the responses (0–24) is the Epworth score. Using a cut-off of >10, the Epworth scores had 93.5% sensitivity and 100% specificity for distinguishing narcoleptic subjects from controls.

The Pittsburgh Sleep Quality Index (PSQI)31 is a self-report questionnaire that evaluates sleep quality and quantity. The original version was designed to assess sleep reports over a 1-month interval. It is a 19-item self-report questionnaire that yields seven component scores: subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. There are five additional questions that are completed by a bed partner, if there is one, although these are not used in the scoring.

The Jenkins’ Sleep Problem Scale evaluates how many times, during the last month, the subject has experienced any of these problems: trouble falling asleep, trouble staying asleep, waking up several times per night, waking up after usual amount of sleep tired and worn out. For each question patient had to indicate the experienced frequency.32

Juniper et al. recently validated the Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire,33 which is specifically designed to assess the functional problems that are most troublesome for patients with nocturnal symptoms of allergic rhinitis. This questionnaire includes 16 items divided into four sections: sleep problems, symptoms during sleep time, symptoms upon waking, and practical problems.

Although numerous specific questionnaires for the assessment of the QoL in allergic diseases contain questions about sleep disturbances only few instruments include a domain specifically addressed to sleep problems (Table 2).34–39

**Respiratory Allergy and Sleep Disturbances**

Allergic rhinitis interferes with restful sleep in several ways: evidence has shown that both symptoms (rhinorrhea, sneezing, nasal pruritus, and nasal congestion) and the underlining pathology can disrupt sleep.40 In addition, nasal congestion at night caused by allergic rhinitis has been linked to OSA in both experimental and clinical studies. In a population-based study, Young et al.31 evaluated the impact of acute and chronic nasal congestion on sleep quality. Of 4927 subjects who completed a questionnaire on nasal congestion and sleep problems, 911 were also assessed using objective laboratory measurements. Compared with asymptomatic subjects, patients who referred frequent rhinitis symptoms (five or more nights a month) were significantly more likely to refer habitual snoring (P < .0001), daytime somnolence (P < 0.001), and nonrestorative sleep (P < 0.0001). Furthermore, subjects with nasal congestion caused by allergic rhinitis were 1.8 times more likely to suffer from moderate-to-severe sleep-disordered breathing compared to those without nasal congestion.

In a prospective evaluation of 39 children with chronic snoring,36 36% were sensitive to allergens, which is about three times the prevalence in nonsnorers. In addition, the frequency of OSAS was increased in subjects with positive radioallergosorbtent tests (RAST) compared to those with negative RAST.

In a prospective controlled clinical trial, Stuck et al.37 investigated the impact of seasonal allergic rhinitis (SAR) on objective and subjective sleep patterns, QoL, and daytime sleepiness. Twenty-five patients with SAR and 25 healthy volunteers underwent two consecutive nights of fully attended polysomnography before and during the pollen season. QoL was evaluated using a generic health status measure (SF-36) and daytime sleepiness with the ESS. Statistically significant differences were demonstrated with daytime sleepiness and selected domains of QoL: physical functioning (P < 0.0001), role physical limitation (P < 0.0001), and mental health (P < 0.046). Those results were related to rhinitis severity.
**Fig. 2.** Sleep apnea syndrome screening throughout airway flow evaluation. Black signal = snoring; red label = apnea; light blue label = hypopnea.

**Fig. 3.** Polysomnogram representing obstructive sleep apnea. Apneas are highlighted by red underline.
Recently, a large survey involving 2355 individuals with allergic rhinitis focused on the impact of nasal congestion on patients’ life. More than 80% of the respondents experienced nasal congestion at night, and 17% indicated that this is the most bothersome nocturnal symptom. Indeed, about half the number of patients referred to difficulties in falling asleep and wake up during the night because of nasal congestion, with a relevant effect on partners’ sleep. When analyzed on the basis of severity congestion, sleep was disrupted in more subjects with severe nasal congestion (90%), than those with moderate (83%) or mild (71%) congestion.44

A recent cross-sectional study45 investigated whether wheezing is related to sleep disturbances and increased daytime symptoms in a pediatric population. Parents of 1234 children between 6 and 14 years were asked to compile a questionnaire evaluating six dimensions: difficulty falling asleep, awakening at night, pauses in breathing pattern at night, snoring, restless sleep, and daytime tiredness. In children who wheezed, sleep quality was more frequently impaired than in children without wheezing due to difficulty falling asleep, restless sleep, and snoring. This resulted in nighttime sleepiness and tiredness. In addition, the presence of respiratory symptoms (wheeze, chronic cough, and upper airway symptoms) was found to constitute a risk factor for sleep disturbance, more so than specific diagnosis of respiratory disease. An increased prevalence of snoring and self-reported apnea in asthmatic subjects was also reported in a recent study by Erici et al.46

Across-sectional survey aimed to provide a comprehensive evaluation of sleep problems, QoL, work functioning, and healthcare utilization in chronic diseases, involved 3484 patients with different diagnoses.47 In patients with asthma sleep problems, several dimensions of the SF-36 were significantly affected (physical functioning, role physical limitations, social functioning, role emotional limitations, mental health, and mental component summary). In addition, asthmatic patients with sleep disturbances scored lower than those without sleep disturbances on all scales.

A recent study conducted on 3052 patients consulting general practitioners for allergic rhinitis evaluated the impact of the disease on QoL, sleep, and work productivity.48 Patients were classified according to the four classes of ARIA and compiled three questionnaires: the rhinoconjunctivitis quality of life questionnaire (RQLQ), the Jenkins questionnaire for sleep problems, and work performance as measured by the Allergy-Specific Work Productivity and Activity Impairment (WPAI-AS) questionnaire that measures work performance. Sleep, daily activities, and work productivity were impaired in patients placed in all four ARIA categories, and rhinitis severity was more important than duration.

Nocturnal cough, wheeze, and breathlessness sometimes represent the first symptoms of asthma, and are also nighttime markers of uncontrolled asthma. Nocturnal asthma causes significant sleep disturbance. For more asthmatic patients, the major problem is sleep disturbance and feeling tired during the daytime. Consistently, the physicians involved in a large French survey indicated the impact of dyspnea on daily activities and/or sleeping as a relevant criterion they use to define a mild asthma exacerbation.49 In addition, the therapeutic management of asthma should take into account that the presence of concomitant rhinitis may further impair sleep.50

Polysomnography provides evidence of sleep disruption with decreased sleep efficiency and increased intervening wakefulness and drowsiness.51,52 This probably results in the impaired cognitive function found in patients with nocturnal asthma compared with age-and education-matched control subjects. Therefore, the resulting sleep problems could have marked effects on the work and school performance of patients with nocturnal asthma.

An extensive body of research has demonstrated that nocturnal symptoms (mainly cough and dyspnea) are common

### Table 1. Questionnaires Used for the Assessment of Sleep Problems in Allergic Diseases

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Reference</th>
<th>n Items</th>
<th>About Sleep</th>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickness Impact Profile</td>
<td>Bergner et al. (27)</td>
<td>136</td>
<td>7</td>
<td>12 Sleep and rest</td>
</tr>
<tr>
<td>Nottingham Health Profile</td>
<td>Hunt et al. (28)</td>
<td>45</td>
<td>5</td>
<td>6 Sleep initiaion</td>
</tr>
<tr>
<td>12-item index (Medical Outcome Study)</td>
<td>Stewart and Ware (29)</td>
<td>12</td>
<td>12</td>
<td>5 Maintenance</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>Johns (30)</td>
<td>8</td>
<td>8</td>
<td>– Sleep initiation</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>Buysse et al. (31)</td>
<td>19</td>
<td>19</td>
<td>7 Respiration</td>
</tr>
<tr>
<td>Jenkins’ Sleep Problem Scale</td>
<td>Jenkins et al. (32)</td>
<td>4</td>
<td>4</td>
<td>– Somnolence</td>
</tr>
<tr>
<td>Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire</td>
<td>Juniper et al. (33)</td>
<td>16</td>
<td>16</td>
<td>4 Efficiency</td>
</tr>
</tbody>
</table>

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An extensive body of research has demonstrated that nocturnal symptoms (mainly cough and dyspnea) are common
Allergic Skin Disorders and Sleep Disturbances

O’Donnel et al.\textsuperscript{56} evaluated the degree of disability in patients with chronic urticaria (CU) using 40 questions specifically designed for this condition along with a generic tool (NHP). Focusing on sleep, the study results show that this component is significantly impaired because of CU. Using the specific questionnaires, 38% of patients referred high sleep disruption and a further 54% had some sleep interferences. Relaxation during the day was a major problem for 50% of patients and 41% reported some difficulty. NHP results confirmed that the burden of sleep disturbance is marked and is greater in CU patients compared to patients with ischemic heart disease.

The clinical characteristics of pruritus and its effect on daily life have been evaluated in a group of 100 patients suffering from chronic idiopathic urticaria.\textsuperscript{57} Most patients experienced pruritus at night ($n = 46$) or in the evening ($n = 37$), rather than in the morning ($n = 25$) or at noon ($n = 18$). As a consequence, sleep was disrupted: 64 patients referred being woken up because of their itch, 62 had difficulties in falling asleep, and 13 took sedatives. In addition, 42 patients were more agitated due to the pruritus and 43 reported lack of concentration.

### Table 2. Sample of Specific Questionnaires for Allergic Diseases Including a Domain Related to Sleep Problems

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Reference</th>
<th>n Items</th>
<th>n Scales</th>
<th>Scales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoconjunctivitis Quality of Life Questionnaire</td>
<td>Juniper et al. (36)</td>
<td>28</td>
<td>7</td>
<td>Nasal symptoms, Practical problems, Non-nasal symptoms, Sleep disorders, Activities, Eye symptoms, Emotions, Social/leisure, Sport, Sleep, Holidays, Work and other activities, Colds, Mobility, Effects on others, Medication use, Sex, Dysphoric states, Attitudes</td>
</tr>
<tr>
<td>Living with Asthma Questionnaire</td>
<td>Hyland et al. (39)</td>
<td>68</td>
<td>11</td>
<td>Social/leisure, Sport, Sleep, Holidays, Work and other activities, Colds, Mobility, Effects on others, Medication use, Sex, Dysphoric states, Attitudes</td>
</tr>
<tr>
<td>Childhood Atopic Dermatitis Impact Scale</td>
<td>Chamlin et al. (37)</td>
<td>45</td>
<td>5</td>
<td>Child dimensions, symptoms, activity limitation/behavior, Parent dimensions, family/social function, sleep, emotions</td>
</tr>
<tr>
<td>Chronic Cough Impact Questionnaire</td>
<td>Baiardini et al. (34)</td>
<td>16</td>
<td>4</td>
<td>Sleep/Concentration, Social relationship, Mood, Daily Life Impact, Pruritus, Swelling, Impact on life activities, Sleep problems, Limits, Looks</td>
</tr>
<tr>
<td>Chronic Urticaria Quality of Life Questionnaire</td>
<td>Baiardini et al. (38)</td>
<td>23</td>
<td>6</td>
<td>Pruritus, Swelling, Impact on life activities, Sleep problems, Limits, Looks</td>
</tr>
</tbody>
</table>

in asthma clinical syndrome: as many as 90% of asthmatics experience nocturnal symptoms severe enough to awaken them from sleep.\textsuperscript{53} In a large survey conducted by Turner-Warwick, up to 75% of 7729 asthmatics were awakened by asthma symptoms at least once per week: 64% had symptoms three nights per week, and approximately 40% referred nocturnal symptoms on a nightly basis.\textsuperscript{54} The prevalence of asthma and sleep complaints was also evaluated in community-based study involving 1478 adults. More than 80% of the asthmatic patients, independently of age and young wheezers reported waking at night with wheeze at least occasionally, and more than 30% of each group reported this symptom frequently. A larger percentage of asthmatics and young wheezers referred that their nighttime sleep was nonrestorative, and that they had loss of sleep at night compared with the other respondents.\textsuperscript{49}

The Asthma Insights and Reality in Europe study is a survey that evaluated the level of asthma control in seven European countries involving almost 3500 asthmatic patients.\textsuperscript{55} Out of 2803 respondents to a telephone interview, 28% of children and 30.5% of adults referred asthma-related sleep problems at least once a week. Sleep disturbance every night was reported by 6.7% of children and 5.3% of adults.

### Articles

Sleep Diagnosis and Therapy • Vol 2 No 2 April-May 2007
Quality of life, disturbed sleep and daytime somnolence in patients with atopic dermatitis (AD) were assessed in a study by Bender et al. Fourteen adult patients with AD and 14 healthy subjects were assessed by objective measurements (actigraphy) and completed three questionnaires about sleep (PSQI), QoL (Dermatology Life Quality Index), and itch [visual analog scale (VAS) range from 0 to 100]. Both actigraphy and self-report measurements demonstrated that AD patients slept more poorly and reported more daytime fatigue than controls. The AD score showed significantly higher impairment in three out of eight dimensions of PSQI (awakening, sleep quality, and daytime dysfunction) and in the global score.

A multicenter clinical trial involving 233 patients with asthma, allergic rhinitis, eczema/dermatitis syndrome (AEDS) evaluated the effects of concomitant atopic diseases on the QoL. Along with a generic QoL questionnaire (SF-36), patients completed 4 VAS to score the severity of asthmatic and rhinitic symptoms, itching, and sleepless. As expected, SF-36 scores of atopic patients were lower than those of the control group. Sleeplessness had a significant (P < 0.01) negative impact on physical functioning, role physical limitation, bodily pain, general health, mental health, social functioning, and vitality. An analysis based on a multiple regression model showed that sleep problems were more likely related to the diagnosis of AEDS, and may impact QoL, independently of the disease. These results highlight that sleep problems constitute an independent problem with a negative impact on the QoL in atopic patients.

The Detrimental Effect of Anti-Allergic Drugs on Sleep

In accordance with the new guidelines of the ARIA, H1-receptor antagonists are the first line of treatment for intermittent and persistent rhinitis, occurring alone or in combination with associated airway disorders (asthma, sinusitis, and otitis media). Antihistamines are also widely used in the treatment of urticaria, allergic eczema, and AD syndrome due to their symptomatic and anti-inflammatory effects. The major adverse side effects of first-generation antihistamines have traditionally been sedation, which occurs in as many 10–50% of patients. The medications induce sleep, adversely affect awakening, reduce alertness, and prolong sleep. Such adverse effects can seriously reduce cognitive function (sustained attention, reaction time, cerebral processing) and impair tasks where concentration and a high degree of alertness are required (i.e., driving performance, learning, work). Aliterature review of double-blind placebo-controlled studies with a positive control showed that first-generation antihistamines (diphenhydramine, tripolidine, terfenadine, dexchlorpheniramine, clemastine) significantly affect driving performance after both one-time and repeated (daily) administration. Tolerance develops after 4–5 days of administration, but impairment is not absent.

The influence of diphenhydramine (50, 75, and 100 mg) and lorazepam (0.5 and 1.5 mg) was evaluated in a double-blind, placebo-controlled study with a crossover design including 12 healthy volunteers (six men, six women) aged 20–33 years (mean 23.4). Subjective evaluation of sedation, sleep latencies, digit symbol substitution, choice reaction time, sustained attention, and memory recall were assessed 1.0 h before and 0.5, 2.0 and 3.5 h after drug ingestion. Subjective sedation, reduced sleep latencies, and impairments in performance on the digit symbol substitution, choice reaction time and sustained attention tasks were reported with all doses of diphenhydramine. No effects were observed with 0.5 mg lorazepam. At a dose of 1.5 mg lorazepam there were subjective sedation, fewer digit symbol substitutions, slowed choice reaction time, impaired attention and memory, but no effect on sleep latencies. Contrast analysis of data measured at all time points showed that although there was no difference in the effect of diphenhydramine (100 mg) and lorazepam (1.5 mg) on those tasks without memory involvement, response times were slower with lorazepam on those tasks with a memory component. However, both 100 mg diphenhydramine and 1.5 mg lorazepam had a negative impact on prompted recall, showing that impaired memory is not necessarily related to sedation.

Recently, Theuninsen et al. evaluated 16 healthy volunteers undergoing treatment with mequitazine 10 mg q.a.m., cetirizine 10 mg q.a.m., dexchlorpheniramine Repeatab 6 mg b.i.d. and placebo for four separate 8-day periods. Drug effects were assessed on days 1 and 8 using on-the-road driving tests (highway driving and car following). Dexchlorpheniramine and mequitazine significantly impaired driving performance on the highway driving test on the first day, although the effects on driving performance were no longer present after 8 days of treatment.

The results of a recent study show that patients taking a first-generation antihistamine are at risk of lapses and significant errors that may lead to potential hazards and decreased work productivity. In a randomized controlled trial the initial and steady-state effects of diphenhydramine, a first-generation antihistamine, and loratadine, a second-generation antihistamine, were assessed in 98 healthy volunteers using a comprehensive battery of psychometric tests that mirror real-world tasks. After the initial dose, subjects taking diphenhydramine had poorer cognitive performance compared to subjects taking loratadine or placebo on tasks of divided attention, working memory, speed, and vigilance. Subjects taking diphenhydramine also referred greater fatigue and sleepiness and lower levels of motivation, and rated the quality of their performance lower compared to subjects taking loratadine or placebo. On day 3, subjects taking diphenhydramine continued to present more fatigue and lower motivation, and rated the quality of their test performance as poorer with respect to those taking loratadine or placebo: the overall results were decrements in daily performance and an increased risk of injury. In contrast, a review on the sedative profile of antihistamines clearly showed that second-generation antihistamines represent a major advance in the treatment of allergy in patients who wish to continue with their activities of daily life without experiencing impairment in cognitive or psychomotor abilities.

Conclusion

Sleep disturbances related to allergy have significant implications for disease management and QoL. If it is clear that independent sleep disorders can often coexist with allergy, their presence should be taken into account as they may constitute a risk factor. There is an ongoing need to educate physicians about sleep disorders in allergic diseases, particularly as the prevalence of sleep disturbance is so high that the investigation and management of many patients involve clinicians outside of specialized allergy centers.
Acknowledgments

This study has been partially supported by ARMI A (Associazione Ricerca Malattie Immunologiche e Allergiche), GA3LEN, and MIUR.

References