AAAAI Work Group Report

Role of the Allergist-Immunologist and Upper Airway Allergy in Sleep-Disordered Breathing

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BACKGROUND: Sleep-disordered breathing in general and obstructive sleep apnea in particular are commonly encountered conditions in allergy practice. Physiologically, nasal (or nasopharyngeal) obstruction from rhinitis, nasal polyposis, or adenotonsillar hypertrophy are credible contributors to snoring and nocturnal respiratory obstructive events. Nevertheless, existing practice parameters largely relegate the role of the allergist to adjunctive treatment in cases of continuous positive airway pressure intolerance.

OBJECTIVES: To survey active American Academy of Allergy, Asthma & Immunology members regarding their perceptions and practices concerning sleep-disordered breathing in adult and pediatric patients with rhinitis, and to review the medical literature concerning this connection to identify therapeutic implications and research gaps.

METHODS: Members of the Work Group on Rhinitis and Sleep-disordered Breathing composed and distributed a Web-based clinically oriented survey to active American Academy of Allergy, Asthma & Immunology members in mid-2015. The group, in addition, conducted an English-language literature review using PubMed and other sources.

RESULTS: Survey results were returned by 339 of 4881 active members (7%). More than two-third of respondents routinely asked about sleep problems, believed that sleep-disordered breathing was a problem for at least a "substantial minority" (10%-30%) of their adult patients, and believed that medical therapy for upper airway inflammatory conditions could potentially help ameliorate sleep-related complaints. Literature review supported the connection between high-grade nasal congestion/adenotonsillar hypertrophy and obstructive sleep apnea, and at least in the case of pediatric patients, supported the use of anti-inflammatory medication in the initial management of obstructive sleep apnea of mild-to-moderate severity.

CONCLUSIONS: Clinical allergy practice and the medical literature support a proactive role for allergists in the diagnosis and management of sleep-disordered breathing. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:628-39)

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Sleep-disordered breathing (SDB) spans a spectrum of diseases including snoring, upper airways resistance syndrome, obstructive sleep apnea (OSA), and central sleep apnea. SDB in general and OSA in particular are highly prevalent conditions in adult and—increasingly—in pediatric populations.[1,2] SDB is frequently found as a comorbid condition in upper airway allergy, including in patients with rhinitis and rhinosinusitis.[2-7] In spite of this fact, clinical guidelines from the American Academy of Sleep Medicine for the diagnosis and management of OSA relegate the role of the allergist to that of adjunctive support. Although these guidelines recommend examination for nasal abnormalities ("polyps, [septal] deviation, [nasal] valve abnormalities, turbinate hypertrophy"), medical treatment for rhinitis is recommended only in the context of intolerance to (or ineffectiveness of) continuous positive airway pressure (CPAP) due to high-grade nasal congestion.[8]

The perspective of allergists, however, appears to place more "upstream" emphasis on upper airway allergic conditions. Numerous studies link nasal congestion (airflow obstruction; a cardinal manifestation of rhinitis) with mouth breathing, snoring, and in susceptible individuals, OSA.[9-13] Furthermore, in pediatric populations, adenotonsillar hypertrophy (ATH), a frequent accompaniment to atopy, also adversely affects upper airway function and is linked to OSA, independent of rhinitis

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Abbreviations used
AAAAI- American Academy of Allergy, Asthma & Immunology
ADHD- Attention deficit/hyperactivity disorder
AHI- Apnea-hypopnea index
AR- Allergic rhinitis
ATH- Adenotonsillar hypertrophy
CPAP- Continuous positive airway pressure
NAR- Nonallergic rhinitis
OSA- Obstructive sleep apnea
OSAS- Obstructive sleep apnea syndrome
QOL- Quality of life
SDB- Sleep-disordered breathing

status.[14-19] SDB in children can have profound behavioral consequences, including daytime somnolence and attention deficit/hyperactivity disorder (ADHD), making its early recognition and effective treatment imperative.[20-22] These links between allergy and SDB highlight the possibility that primary treatment for upper airway allergic conditions may help alleviate SDB symptoms by addressing underlying physiologic abnormalities.

Because allergists may have a unique perspective on SDB, and because important research and practice questions may not be widely articulated, the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology (AAAAI) undertook, through its Work Group on Rhinitis and Sleep-disordered Breathing, to (1) survey the AAAAI membership regarding members' experience, attitudes, and clinical practice regarding SDB in adult and pediatric patients with rhinitis and (2) review the published literature on rhinitis, rhinosinusitis, and ATH and its link to SDB. The objective of this project was to serve as an evidence-based resource for providers as they choose among diagnostic and management options, as well as to help prioritize future research needs on the basis of identified literature gaps.

AAAAI MEMBERSHIP SURVEY

A 16-item questionnaire was drafted by the work group and in mid-2015 was distributed electronically to 4881 AAAAI members. The questionnaire asked respondents to indicate their scope-of-practice (adult, pediatric, or both), and, depending on the response to this question, presented them with a series of patient-age—appropriate questions pertaining to their clinical experience and diagnostic and therapeutic practice.

Responses were received from 339 members (7%), including 293 from the United States, 14 from Canada, and 32 from other countries. Of the respondents, the vast majority (82%) treated both adults and children, with 9% each treating children or adults only. Results appear in Tables I-IV. Give the relatively low response rate and the fact that a comparison of the practice characteristics of responders and nonresponders was not possible, it is conceivable that responders self-selected on the basis of their level of interest in this clinical topic.

To summarize, 72% of respondents routinely asked about sleep quality, although only 14% reported using paper-and-pencil screening tests in suspected SDB (Table I). Seventy-two percent of respondents also perceived that at least a "substantial minority" (10%-30%) of their adult patients with allergy manifested symptoms of SDB, and 70% "often" deferred polysomnography pending possible symptomatic response to medical treatment (Table II). Among respondents evaluating children with suspected OSA and ATH, 60% used anti-inflammatory medication as initial therapy, although most managed cases in collaboration with an otolaryngologist (Table III). Overall, 71% of respondents believed that allergy medication improved sleep quality in at least a "substantial minority" (10%-30%) of their patients; a smaller percentage (44%) believed that immunotherapy was helpful in this regard. Finally, 73% believed that medical therapy improved CPAP tolerance in at least a subset of patients with rhinitis (Table IV). The attitudes and practices reflected in this limited sample of respondents reflect a more active emphasis on the role of the allergist in SDB than do published sleep guidelines.

TABLE I. Survey results: Practice characteristics of 339 responding AAAAI-member allergists/immunologists

Characteristic	n (%)
Country of residence	
United States	289 (86)
Canada	14 (4)
Other	33 (10)
Age group treated	
Adult + pediatric	277 (82)
Adult only	32 (9)
Pediatric only	30 (9)
Routinely query SDB symptoms?	
Yes	241 (72)
No	96 (28)
Use hardcopy screening tools?	
Yes	48 (14)
Epworth	36 (10)
STOP-BANG	2 (1)
Other	1 (3)
No	289 (86)

STOP-BANG, Snore, Tired, Observed (apnea), high blood Pressure, Body mass index, Age, Neck circumference, and Gender.

LITERATURE REVIEW

The literature review began with an English-language PubMed search (("obstructive sleep apnea" OR "sleep-disordered breathing") AND (rhinitis)) conducted in October 2014, initially yielding 59 relevant references, which was augmented with pediatric (and other) citations familiar to the coauthors, as well as selected interim publications discovered during the 18 months of project activity. The literature summary that follows is a collective project organized by subject—including prevalence and demographic characteristics, pathophysiology, clinical evaluation and management, and unique pediatric considerations.

Prevalence and demographic characteristics

SDB is a common manifestation in metabolic syndrome, but is not limited to those who are elderly, obese, diabetic, hypertensive, and with cardiac disease.[23,24] In the elderly, SDB is seen in as many as 60% of individuals studied. The prevalence is much lower in children and young adults. In general, the prevalence of SDB in children is estimated to be approximately 2%; however, many think this is a gross underestimation because of a lack of consensus of the diagnostic criteria for SDB in children.[25] Furthermore, in certain cohorts, such as those with craniofacial abnormalities, Downs syndrome, ATH, obesity, and rhinitis, the

TABLE II. Survey results: Practice experience—Adults

Question	n (%)
Proportion of rhinitics with SDB?	
Small minority (<10%)	80 (28)
Substantial minority (10%-30%)	175 (60)
Many or most (>30%)	35 (12)
Subsets at greater risk of SDB?	
Yes—Allergic rhinitics	49 (17)
Yes—Nonallergic rhinitics	21 (7)
No—Equal risk	139 (48)
No opinion	82 (28)
Defer PSG pending response to empirical rhinitis therapy?	
Yes	203 (70)
No	87 (30)
Directly order PSG?	
Yes	96 (33)
No	196 (67)
Refer based on PSG results?	
Yes	57 (20)
No	78 (27)
NA	151 (53)
Order home PSG?	
Yes	62 (21)
No	230 (79)

NA, Not applicable/available; *PSG*, polysomnography.

TABLE III. Survey results: Practice experience—Pediatrics

Question	n (%)
How assessed for ATH?	
Endoscopy	11 (4)
Radiography (plain film or CT)	106 (36)
Refer to ORL	181 (60)
Initial therapy for ATH?	
Refer to ORL for surgery	109 (37)
Rx steroids/montelukast	176 (60)
Skin test & immunotherapy PRN	9 (3)

CT, Computed tomography; *ORL*, otorhinolaryngologist; *PRN*, pro re nata - when necessary.

TABLE IV. Survey results: Practice experience—Adults + pediatrics

Question	n (%)
"Among atopic patients with SDB symptoms…"	
Allergy medicines improve sleep quality:	
Small minority (<10%)	63 (20)
Substantial minority (10%-30%)	121 (39)
Many or most (>30%)	100 (32)
NA	25 (8)
Immunotx improves sleep quality:	
Yes—Adult + pediatric	124 (40)
Yes—Adult only	8 (3)
Yes—Pediatric only	5 (1)
No	69 (22)
NA	101 (33)
"Among atopic patients w/OSA who are treated with CPAP…"	
Compliance improved w/allergy Tx?	
Yes—In most cases	132 (40)
Yes—In select cases	103 (33)
No	82 (27)
How treat CPAP intolerance?	
Nasal steroids	290 (86)
Nasal antihistamines	182 (54)
Nasal ipratropium	70 (21)
Nasal irrigation (saline solution)	211 (62)

Immunotx; Immunotherapy; *NA*, not applicable/available; *Tx*, treatment.

condition is believed to be more common than in the general pediatric population.

Allergic rhinitis (AR) is thought to affect up to 40% of the population, and its prevalence is increasing worldwide.[26] About 80% of people with AR are symptomatic before the age of 20 years, and the overall prevalence of AR in children is reported to be 40%.[27,28] AR can be categorized as perennial/persistent or seasonal/intermittent on the basis of allergen sensitivity and timing of the inflammatory stimulus; however, frequently both occur together leading to year-round congestion.[29] Typically, the most common SDB seen in children is snoring, but micro-arousals, hyponea, and apnea have also been associated with rhinitis-related nasal obstruction, inflammatory mediators, and other rhinitis sequelae.[30,31]

Allergy-induced nasal congestion has a large impact on sleep in both children and adults. The 2009 Pediatric Allergies in America survey emphasized that nasal congestion is the most reported symptom affecting children.[32] In the same survey, 26% to 40% of parents perceived a negative impact of allergies on their children's sleep. In adults, the 2009 Burden of Rhinitis in America survey indicated that sleep disturbance played a major negative role in patients with rhinitis, with less than 5% of the almost 4000 AR sufferers surveyed experiencing 100% sleep adequacy.[33] In a recent survey of individuals with AR, 68% of respondents with perennial AR and 48% with seasonal AR reported that their condition interfered with sleep.[33-35] Overall, sleep impairment is a significant problem for patients with AR, and nasal congestion is one of the main causes.

SDB is not limited to AR, but nonallergic rhinitis (NAR) can also predispose to SDB. Recent work by Krakow et al[36] has demonstrated an enrichment of patients with NAR in a community-based sleep medical center. The rate of NAR was more than twice that expected as compared with the general population. Up to 70% of the patients with congestion had NAR.

As noted above, and depending on methods used and populations surveyed, rhinitis has a prevalence of 15% to 40%, and more than 50% of these individuals have congestion as their main symptom. Even more concerning are the effects of congestion on those who experience it. Stull et al[37] concluded that congestion alone accounted for 73% of the adverse outcomes associated with AR, including poor sleep, missed work, and activity impairment. Congestion had a much greater effect on patients than any other symptom of rhinitis assessed. According to individuals in this cohort, 30% of impaired sleep was secondary to congestion.

Pathophysiology

OSA is thought to occur most often as a result of events in the upper airway. Although attention generally focuses on the

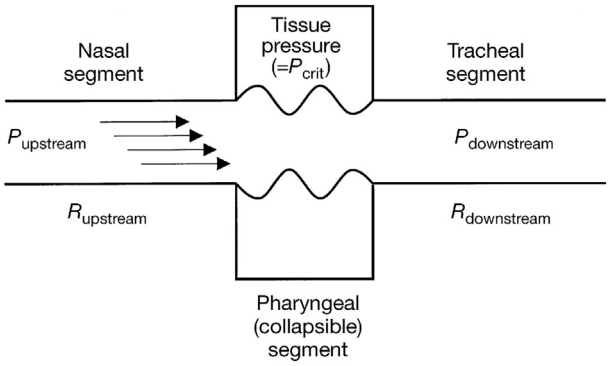

FIGURE 1. The Starling resistor model of upper airway in obstructive sleep apnea. Increased nasal airway resistance ($R_{upstream}$, from reversible or nonreversible causes) augments the likelihood that pharyngeal pressure will fall below the critical pressure for pharyngeal closure (P_{crit}), thereby precipitating obstructive event(s). Reprinted from Hillman DR, Platt PR, Eastwood PR. The upper airway during anaesthesia. Br J Anaesth 2003;9:31-39, by permission of Oxford University Press.

retroglossal space (oropharynx) as the collapsible segment in OSA, nasal (and nasopharyngeal) function can nevertheless be an important factor. Several mechanisms connect impaired nasal function to worsened SDB. These include the effect of nasal resistance on pharyngeal patency (as explained by the Starling resistor model), the role of unstable oral breathing (generally precipitated by nasal obstruction), and central effects mediated by the nasal-ventilatory reflex.

Although the primary area of obstruction in OSA is the pharynx, upstream nasal resistance can modify downstream pharyngeal airflow.[38] Based on the Starling resistor model (Figure 1), maximum airflow is described by the following equation[39]:

$$\text{Flow or } V_{\text{maximum}} = (\text{Pressure}_{\text{nasal}} - \text{Pressure}_{\text{critical}})/\text{Resistance}_{\text{nasal}}$$

This relationship reflects the fact that an increase in nasal resistance limits flow through a collapsible downstream pharyngeal segment.[40] Further exacerbating airflow limitation, an increase in airflow velocity may trigger the Bernoulli effect and cause paradoxical airway narrowing (more commonly in the nasal valve but, as obstruction progresses, also in the oropharynx). Underlying this collapsibility, the pharyngeal dilator muscles are hypotonic during sleep, predisposing to pharyngeal narrowing. As such, there is a critical pressure at which the oropharynx will collapse, defined as the $\text{Pressure}_{\text{critical}}$ (P_{crit}). An alternate way of thinking about this is that the P_{crit} is the pressure necessary to overcome the obstruction precipitated by negative inspiratory pressure. Therefore, assuming pharyngeal recoil cannot compensate for upstream pressure drops, P_{crit} is also the minimum therapeutic CPAP required to keep the retroglossal pharynx patent.[41]

Several studies have found an increase in nasal resistance in OSA, correlating with apnea severity in some studies[42] but not in others.[43] Lofaso et al[44] provided evidence via posterior rhinomanometry that nasal obstruction independently correlated with OSA severity. In subjects with AR to ragweed, obstructive apneas were longer and more frequent during ragweed season than after the pollen season.[45] Furthermore, nasal obstruction appears to have a synergistic effect when combined with poor oropharyngeal patency as defined by elevated Mallampati indices. (The Mallampati index, ranging from class 1 to 4, summarizes the appearance of the posterior tongue, soft palate, and tonsillar pillars on physical examination, with higher class number indicating a greater degree of apparent oropharyngeal obstruction.[46-49]) In 2 studies, decreased space in the posterior pharynx was associated with sleep apnea, particularly in those with nasal obstruction.[50,51] Liistro et al[51] proposed a 2-hit phenomenon, with a higher relative risk for OSA in those with both high Mallampati indices and nasal obstruction compared with the former alone.

Physiologically, nasal breathing is advantageous during sleep compared with mouth breathing. Mouth breathing, most often precipitated by nasal congestion, is associated with 2.5 times higher total airway resistance.[52] To a significant degree, this difference relates to the posterior displacement of the tongue base during mouth breathing,[53] as well as instability precipitated by oral airflow between the tongue and the soft palate. Further upstream, the internal nasal valve, bordered by the septum, the head of the inferior turbinate, and the lower edge of the upper lateral cartilage, is responsible for more than 50% of total respiratory resistance.[54] As a rate-limiting upstream segment, the nasal valve is sensitive to vascular changes in the inferior turbinate, including those related to the nasal cycle, recumbent sleep position, allergic inflammation, and neurohumoral factors.[55] In addition, an incompetent external nasal valve can collapse during inspiration. During sleep, ventilation occurs preferentially via the nasal route, absent a pathological degree of nasal obstruction due to reversible (eg, allergic) or nonreversible (ie, anatomic) factors.

Besides narrowing the anteroposterior diameter of the retroglossal space, other disadvantages accrue from mouth breathing. Mouth breathing disrupts upper airway dilator muscles' length-tension relationships.[56] When the mandible is displaced inferior-posteriorly, the dilator muscles are thought to have a poor length-tension curve leading to mechanical inefficiency. In childhood, disorders such as AR and adenoid hypertrophy can increase nasal (or nasopharyngeal) resistance and lead to mouth breathing. The craniofacial structure may also be permanently altered with a high arched palate and elongated facies. Regardless of the underlying cause, mouth breathing alters functional anatomy, causing the tongue and mandible to be positioned posteriorly, and in turn leading to airway obstruction.[39]

Beyond the resistive effects of nasal congestion or abnormal nasal anatomy, the nasal-ventilatory reflex has been shown to centrally mediate some nocturnal respiratory effects. Nasal receptors triggered by mucosal cooling during normal nasal breathing positively influence respiratory rate and minute ventilation.[57] Experimentally blocking the nasal mucosal receptors with local anesthetics in healthy volunteers causes an increase in both central and obstructive apneas.[58]

In sum, multiple lines of evidence provide insight into the mechanisms underlying the connection between nasal pathophysiology and SDB/OSA. These mechanisms may be particularly important in subgroups of patients. Further research is needed to define potential relevant subgroups and to determine whether phenotypic subsetting can help optimize therapeutic interventions.

Clinical evaluation and management

Clinical evaluation. As noted at the beginning of the article, there are established clinical guidelines for the diagnosis and

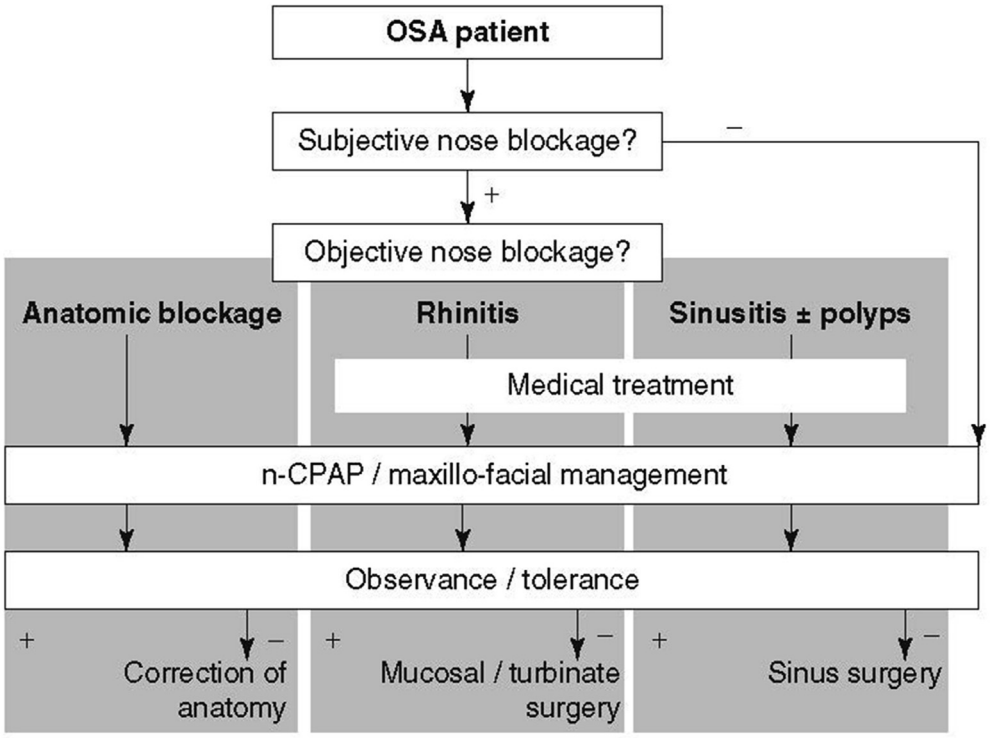

FIGURE 2. Simplified management scheme for adults with OSA. Reprinted from Poirrier A-L, Eloy P, Rombaux P. Nose and sleep breathing disorders. In: Önerci TM, editor, Nasal physiology and pathophysiology of nasal disorders. Berlin, Germany: Springer-Verlag; 2013:293-311, with permission of Springer.

management of OSA, with polysomnography serving as the diagnostic "criterion standard."[8] As part of these guidelines, the need to rule out pathological upstream resistance due to anatomical obstruction is acknowledged, with recommendations to examine for nasal polyps, septal deviation, nasal valve abnormalities, and turbinate hypertrophy. (To these, we would add neoplasms for adult patients, and foreign bodies, congenital malformations, and ATH for pediatric patients.) Besides a thorough history, potential diagnostic procedures may include anterior rhinoscopy, nasal endoscopy, and diagnostic imaging (with potential adjunctive documentation of nasal patency using nasal inspiratory peak flow, rhinomanometry, or acoustic rhinometry).

Missing from published organizational guidelines is consideration of the most common cause of *reversible* nasal obstruction, namely [allergic and nonallergic] rhinitis. Although a discussion of the relative merits of *in vivo* versus *in vitro* allergy testing (or consideration of the relatively recently described phenomenon of "local allergic rhinitis") is beyond the scope of our discussion (and perhaps redundant for this journal's readership), it is worthwhile considering, graphically, the influence of upper airway differential diagnosis on the subsequent therapeutic approach to OSA (Figure 2).

Treatment of OSA and interface with rhinitis. Published recommendations for the treatment of OSA differ between adults and children, but generally consider the medical treatment of reversible nasal obstruction as adjunctive to CPAP treatment (Table V). In a clinical practice guideline reviewing the evidence related to the treatment of OSA in adults, the American College of Physicians strongly recommended, on the basis of moderate-quality evidence, CPAP treatment as initial therapy.[59] The guideline also recommended mandibular advancement devices as an alternative to CPAP therapy in patients who prefer these devices or have CPAP-related side effects. The latter was a weak

TABLE V. Published clinical practice guidelines on obstructive sleep apnea

Organization	Recommendation
ACP (Qaseem et al[59])	"Evidence from 7 RCTs … showing that drug therapy … is superior to control treatment of OSA was insufficient."
ASSM (Epstein et al[8])	"Topical nasal corticosteroids may improve the AHI in patients with OSA and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for OSA."
CTS (Fleetham et al[60])	"Relief of nasal obstruction should not be viewed as a primary treatment of OSAS, but as an adjunct to CPAP."
AAP (Marcus et al[61])	"Clinicians may prescribe intranasal corticosteroids for children with mild OSAS in whom adenotonsillectomy is contraindicated; … nasal steroids are not recommended as a first-line therapy."

AAP, American Academy of Pediatrics; *ACP*, American College of Physicians; *ASSM*, American Society for Sleep Medicine; *CTS*, Canadian Thoracic Society; *RCT*, randomized controlled trial.

TABLE VI. Medical therapy in adults with sleep disorders

Author	Rx	Duration	Population	Design	Results
Lavigne et al[62]	Mometasone furoate 200 μg twice daily	10-12 wk	Patients with OSA with (n = 34) and without (n = 21) AR	Prospective study (non−placebo-controlled)	Objective polysomnographic measures were similar between the groups at baseline except for supine AHI, which was significantly higher in the allergic patients. AHI did not improve significantly after treatment in the combined group. Treatment reduced the AHI in the supine position in allergic subjects significantly more than it did in nonallergic subjects. Significant reduction in CD4 lymphocytes and eosinophils in biopsies of the inferior turbinate, nasopharynx, and uvula in the allergic group
Meltzer et al[63]	Mometasone furoate 200 μg daily	4 wk	Patients (n = 30) with perennial AR and rhinitis-disturbed sleep	Prospective, double-blind, placebo-controlled, parallel	No significant reduction in AHI. Significant improvements in nasal symptoms, the Epworth Sleepiness Scale, and impairment in daily activities in the active treatment group
Acar et al[64]	Mometasone furoate (100 μg daily) desloratadine (5 mg daily)	6 wk	Patients (n = 80) with OSA and AR (positive symptoms and RAST test)	Randomized, double-blinded, double-dummy, placebo-controlled	Significant reduction in AHI, improvement in desaturations, and improvement in Epworth Sleepiness Scale score with mometasone furoate irrespective of added antihistamine. No significant effects on the parameters with desloratadine alone
Kiely et al[65]	Fluticasone propionate 100 μg twice daily	4 wk	Patients (n = 23) with history of loud snoring and symptoms compatible with either perennial or seasonal rhinitis. Divided into 2 groups on the basis of the presence of OSA by PSG	Randomized, double-blind, placebo-controlled, crossover design	Significant reduction in AHI and nasal airflow resistance after fluticasone treatment in the total population. Changes in AHI and nasal resistance were significantly correlated ($r = 0.56$; $P = .05$) in the group with snoring and abnormal PSG. Subjective improvements in nasal congestion and daytime alertness with fluticasone. No change in snoring noise and sleep quality
Craig et al[66]	Fluticasone propionate 200 μg daily	4 wk	Patients (n = 32) with perennial AR	Double-blind, placebo-controlled study	Fluticasone led to a significant improvement in subjective sleep parameters but not in the AHI

PSG, Polysomnography; *RAST*, radioallergosorbent test; *Rx*, treatment regimen.

recommendation because it was supported only by low-quality evidence. An earlier clinical guideline for the evaluation and management of OSA in adults was published by the American Academy of Sleep Medicine and offers similar recommendations suggesting involving the patient with OSA in the management decisions.[8] These include positive airway pressure, oral appliances, behavioral treatments, surgery, and/or adjunctive treatments such as bariatric surgery, oxygen therapy, or medications such as intranasal steroids (nominally to improve CPAP tolerance). A practice guideline from the Canadian Thoracic Society likewise limits the recommendation for intranasal steroids as adjunctive to CPAP.[60] In contrast, the first- line treatment of OSA in children with ATH is adenotonsillectomy, with CPAP recommended if adenotonsillectomy is not performed or if OSA persists postoperatively.[61] Intranasal corticosteroids or leukotriene antagonists are recommended as an option for children with mild obstructive sleep apnea syndrome (OSAS) in whom adenotonsillectomy is contraindicated or for mild postoperative OSAS.

Anti-inflammatory medications—including intranasal corticosteroids in adults and children and leukotriene antagonists in children—have also been used as sole treatment of OSA, although at times showing greater improvement in subjective symptoms than in apnea-hypopnea index (AHI) in published studies (Table VI[62-66] and Table VII[15,20,67-70]). In an adult study, the AHI was reduced 8 points, a 40% reduction, with

TABLE VII. Medical therapy for children with sleep disorders

Author	Rx	Duration	Population	Design	Results
Brouillette et al[67]	Fluticasone propionate (100 μg twice daily for the first week and once daily for 5 wk)	6 wk	Children (n = 25) with OSA (allergic status not specified)	Randomized, triple-blind, placebo-controlled, parallel-group	The mixed/obstructive apnea/hypopnea index decreased significantly in the fluticasone group compared with placebo. The frequencies of hemoglobin desaturation and respiratory movement/arousals also decreased more in the fluticasone group. Changes from baseline in tonsillar size, adenoidal size, and symptom score were not significantly different between groups
Chan et al[68]	Mometasone furoate 200 μg once daily	4 mo	Children (n = 50) with mild OSA (allergic status not specified)	Randomized, double-blinded, placebo-controlled trial	Significant reduction in obstructive AHI and oxygen desaturation index in the active treatment group only
Kheirandish-Gozal and Gozal[15]	Budesonide 64 μg daily	6 wk	Children (n = 62) with mild sleep apnea (allergic status not specified)	Randomized, placebo-controlled, double-blind, crossover trial	Significant improvements in AHI, nadir pulse oxygen saturation, and adenoid size among the 48 children who completed the treatment phase compared with 32 children who received placebo in their initial arm, with normalization of sleep measures in 54.1% of the treated children. Discontinuation of treatment for 8 wk for 25 children revealed a sustained duration of the initial treatment effect
Mansfield et al[20]	Budesonide 128 μg once daily	6-7 wk	Children (n = 14) with perennial AR with seasonal exacerbations, which is typical for our region	Open clinical trial with objective and subjective assessments	Significant decrease in the mean number of sleep arousals per hour (all apneas and hypopneas). The change was mainly in hypopneic episodes. Significant improvements in Rhinitis Quality of Life measures reflecting sleep and rhinitis symptoms
Goldbart et al[69]	Montelukast daily: 4 mg (children younger than 6 y), 5 mg (children 6 y and older)	16 wk	Children (n = 24) with SDB (allergic status not specified)	Open-label intervention study	Significant reductions in adenoid size and obstructive AHI in children who received montelukast therapy. No change in untreated children
Goldbart et al[70]	Montelukast daily: 4 mg (children younger than 6 y), 5 mg (children 6 y and older)	12 wk	Children (n = 46) with OSA (allergic status not specified)	Prospective, double-blind, placebo-controlled, randomized trial	Significant improvements in obstructive apnea index, children's symptoms, and adenoid size in those receiving montelukast

fluticasone, along with improvement in nasal resistance.[65] Most of the studies were performed in patients with mild OSA. Many of these studies did not differentiate between patients with AR and patients with NAR, but because these treatments are approved and effective for the treatment of AR, it is presumed that at least part of their efficacy is related to improving nasal obstruction. Other studies have shown the beneficial effects of intranasal steroids on nasal congestion and subjective sleep parameters (somnolence, daytime fatigue and sleepiness, and quality of sleep) in patients with AR.[71-73] The other rationale for administering intranasal steroids in OSA is a reduction in adenoid size in children, which has been documented in multiple clinical trials.[74,75] Montelukast has also been investigated in children after studies showed increased expression of leukotriene receptors in the tonsils of children with OSA compared with those with recurrent adenotonsillitis.[69,76] The results of both an open-label and a placebo-controlled trial show an improvement in polysomnography parameters coupled with a reduction in adenoid size (Table VII).[69,70] Furthermore, a combination of intranasal budesonide and oral montelukast has been shown to improve residual OSA in children after adenotonsillectomy in an open-label trial.[77]

In the aggregate, the above data paint a slightly different picture than did a 2011 Cochrane Review titled "Anti-inflammatory medications for obstructive sleep apnea in children." Based on the requirement that studies be randomized clinical trials in which OSA status was validated with polysomnography, data were considered only from an intranasal budesonide trial,[15] an oral montelukast trial (data then in abstract form[70]), and an intranasal fluticasone trial.[67] For summary purposes, the first 2 studies were subsequently disregarded because of differential drop-out[15] and incomplete data analysis.[70] The authors' conclusions (based solely on the fluticasone study) were as follows: "A single small study has found a short-term beneficial effect on the AHI in children with mild-to-moderate OSA. However, long-term safety and efficacy data are not available yet. Further RCTs are needed to evaluate anti-inflammatory drugs for OSA in children."[78] Subsequent analysis of the montelukast study showed significant treatment-related benefits (decreased AHI, improved symptoms, and decreased radiographic adenoidal size[70]) and a separate RCT published in 2015 found similar beneficial effects from intranasal mometasone.[68]

Nasal decongestants have also been investigated for the treatment of OSA, with 1 of 4 studies showing a significant reduction in AHI on active therapy and another showing a reduction only during the active portion of the treatment.[79-82] Because of the known concerns with rhinitis medicamentosa, the duration of treatment in these trials was short (1-4 nights in 3 trials and 2 weeks in 1 trial) and these agents are not effective options for long-term therapy. However, these studies are consistent with a pathophysiological link between nasal congestion and SDB.

As mentioned above, CPAP is mainstay in the treatment of adults with OSA. Because this involves the application of air through the nose, some patients suffer from nasal irritation and dryness during therapy.[83] Skoczynski et al[84] counted leukocytes collected by nasal lavage in a group of patients with OSA on CPAP and used 2 control groups for comparison. Compared with the controls, there was a significant increase in total leukocyte count in nasal lavages after 3 days of CPAP in the OSA group with no concomitant change in rhinomanometry measurements. Supportive data come from a study in rats showing neutrophilic nasal inflammation after CPAP therapy.[85] Complicating the causal logic, a third study shows that neutrophils in nasal smears *before* treatment suggest poor compliance to CPAP.[86] In support of these observations, a prospective study following patients with AR and NAR on CPAP for OSA has shown an inverse correlation between CPAP compliance and nasal symptoms, suggesting that worse nasal symptoms negatively impact CPAP compliance.[87] Nevertheless, intranasal fluticasone propionate was not found to reduce CPAP-induced nasal side effects, or improve CPAP compliance during the first 4 weeks of treatment in unselected patients with OSAS.[88] In that study population, AR was present in 7% to 10% of the subjects studied. In another study, 125 patients (allergy status not defined) with OSA tolerating CPAP were treated with additional humidification or fluticasone propionate.[89] The addition of humidification but not intranasal steroids decreased the frequency of nasal symptoms in these patients without any effects on compliance and quality of life (QOL). It is possible that more beneficial effects of intranasal steroids in facilitating CPAP use could be shown in purely allergic populations, but there is currently no evidence to support that claim.

Surgery for OSA. The adult guidelines for the treatment of OSA suggest considering primary surgical treatment in patients with mild OSA who have severe obstructing anatomy that is surgically correctible (eg, obstructive tonsillar hypertrophy).[8] Surgical procedures can also be considered when the outcome of positive airway pressure therapy is inadequate, when there is an inadequate treatment outcome with an oral appliance, or as an adjunct therapy when obstructive anatomy or functional deficiencies compromise other therapies, especially positive airway pressure.[8] As relates to our discussion, many nasal surgeries are considered for the above purposes and they usually address nonreversible causes of nasal obstruction, which include nasal septal deviation, hypertrophy of the mucosa of the inferior turbinates, nasal valve collapse, and nasal polyposis. The most common of these procedures is septoplasty with or without turbinate reduction, which can be achieved by multiple techniques, which include laser, radiofrequency, electrocautery, microdebrider, or submucous resection. Unfortunately, when one reviews the literature, most of these reports are case series and the results, for the most part, suggest an improvement in subjective symptoms of snoring but not in objective polysomnographic parameters (which is seen only in few studies[90-94]). In contrast, when these procedures are performed to facilitate CPAP, the results suggest an improvement in tolerance and compliance with CPAP use after surgery.[95-97]

Although additional randomized controlled studies are needed (particularly for adult OSA), it seems clear that there is a potential treatment role for improving nasal and/or nasopharyngeal obstruction in patients with OSA. The allergist—at times in collaboration with the otolaryngologist—is ideally qualified to address this issue.

Unique pediatric considerations

The prevalence of—and treatment for—childhood OSA has been reviewed in previous sections. This section further addresses pathophysiology, QOL, and behavioral issues in pediatric patients with OSA.

Pathophysiology of SDB in children. Adenoidal hypertrophy or ATH is a frequent source of upstream

(nasopharyngeal) airflow obstruction in children, potentially leading to mouth breathing, snoring, and OSA. Clinical studies suggest that AR is a risk factor for ATH in children.[17,98] The palatine tonsils and adenoids (pharyngeal tonsil) lie just below and behind the nasal airway, respectively. They are part of Waldeyer's ring, which consists of lymphoid cells providing an immunologic response to antigens and inflammatory stimuli present in the nasopharynx. They may, therefore, hypertrophy in response to allergic and other inflammation associated with chronic rhinitis, particularly in childhood when lymphoid processes are most active. Adenotonsillectomy is the most common operation in young children with SDB, although specific mechanisms involved in the development of ATH appear to be diverse.[17]

In a 1-year study by Sadeghi-Shabestari et al,[98] a case group consisting of 117 children aged between 1 and 14 (average age, 6 years) years with ATH and a control group of 100 children of similar age without ATH were compared. Seventy percent of children with ATH, but only 10% of children in the control group, had positive skin prick test results. Increased serum total IgE level was confirmed in 48% of children with positive skin prick test results in the study group. The conclusion was that allergy and sensitivity to multiple allergens are important risk factors for ATH in children.

AR, SDB, and QOL. Eighty-eight percent of children with AR are estimated to experience difficulty sleeping associated with poor learning performance, productivity, and behavior.[12,32] As noted above, the 2009 Pediatric Allergies in America survey revealed that 26% to 40% of parents believed that allergies affected their child's sleep, primarily due to nasal congestion; this compared with only 7% of parents of children without AR. Furthermore, parents of children with AR were more than twice as likely to describe sleep problems, such as difficulty in falling asleep, waking during the night, and lack of a good night's sleep in their children compared with parents of children without AR. Children with AR were also less likely to be described as "happy," "calm and peaceful," "have lots of energy," and "be full of life." Parents also felt that allergies had a negative effect on performance in sports, school, and other activities. Thus, both the pattern and the quality of sleep, as well as the overall QOL, were affected by AR in children.[32]

SDB and behavior. On the basis of parental report questionnaires, Bonuck et al[99] found effects of SDB symptom trajectories from 6 months to 7 years on subsequent behavior. Early trajectories predicted problematic behavior at 7 years equally well as at 4 years. Conclusions were that in this large, population-based, longitudinal study, early-life SDB symptoms had strong, persistent significant effects on subsequent behavior in childhood. In another study, based on parental response to a sleep questionnaire for 70 patients at a child psychiatry clinic and 73 general pediatric patients aged 2 to 18 years, habitual snoring was reported to be 3 times more common in children with ADHD (33%) than in other child psychiatric (11%) or general pediatric populations (9%).[100] However, among 113 children aged 2 to 18 years referred to a university sleep laboratory for suspected SDB, hyperactivity scores were no higher among children with confirmed SDB than in those in whom SDB was ruled out, and scores bore no relationship to AHI, oxygen desaturations, or negative esophageal pressure. Hyperactivity scores, were, however, related to periodic leg movements during sleep, but only among children with ADHD.[101]

In another, school-based study of first graders, parents completed a questionnaire asking about sleep quality and about symptoms consistent with ADHD; a response rate of 47% was achieved.[102] On a pooled basis, frequent and loud snoring was reported by the parents of 12% of children, and behaviors consistent with ADHD by 7%. Among 83 suspected children with ADHD and 34 controls who completed polysomnography, the authors concluded that "no sleep variable accounted for more than a negligible proportion of the variance in domains of neurobehavioral function."[102]

Brawley et al[22] studied patients aged 5 to 18 years who presented with a diagnosis of ADHD to an outpatient pediatric psychiatry clinic and were screened for AR with focused history, physical examination, and skin prick testing to common aeroallergens. Eighty percent reported AR symptoms, whereas 61% had at least 1 positive prick skin test result. Forty-three percent showed typical physical signs of AR, 100% had a positive atopic family history, and 53% had other associated atopic disorders. Although no control group was used in this study, the prevalence of rhinitis in this group of patients is higher than that in the published literature.[22]

In the aggregate, published findings linking SDB with behavior disorders are mixed, and suffer from multiple potential sources of bias. Higher quality studies are needed to clarify this question.

CONCLUSIONS (IMPLICATIONS FOR RESEARCH AND EVIDENCE-BASED PRACTICE)

Increasing evidence implicates AR in adults and children as a contributing factor to SDB. Nasal and/or nasopharyngeal obstruction predispose to mouth breathing, snoring, and oropharyngeal airflow obstruction. OSA, in turn, can have profound physiologic, behavioral, and QOL impacts on affected individuals.

A survey of practicing allergists confirms the importance of OSA in everyday practice, and further highlights the importance of treating nasal conditions as part of an integrated response to this condition. Existing practice parameters for adult patients relegate the role of the allergist to adjunctive treatment after institution of CPAP, and in doing so underemphasize "upstream" events in OSA. Many survey respondents, however, endorse empiric treatment of upper airway allergy in SDB early in the diagnostic and treatment sequence. The scientific evidence supporting such an approach is suggestive, but incomplete. To the extent that data are lacking, the following research questions are worthy of additional attention:

1. In a representative population of adults with OSA of mild-to-moderate severity, what is the relative contribution of elevated nasal airway resistance versus pharyngeal collapsibility to the genesis of obstructive events?
2. Among patients with OSA with high-grade nasal obstruction, what proportion is reversible (eg, allergic) versus nonreversible (ie, anatomic)?
3. Among adult patients with OSA of mild-to-moderate severity who have reversible high-grade nasal obstruction, what is the therapeutic efficacy of allergy treatment, absent CPAP?
4. Among adult patients with OSA of mild-to-moderate severity who have nonreversible high-grade nasal obstruction, what is the therapeutic efficacy of surgical treatment (eg, nasal valve

correction, septoplasty, and turbinate reduction), absent CPAP?
5. What is the value of, and which subgroups benefit most from, nasal allergy therapy (including topical nasal steroids, nasal saline rinses, and specific allergy therapy) on improving CPAP mask intolerance?
6. What is the epidemiology and pathophysiology of CPAP-induced rhinitis?
7. Additional population-based studies defining the prevalence of [allergic and nonallergic] rhinitis among adult and pediatric patients with OSA would benefit progress in this field.

Our review of the pediatric literature reveals a growing body of evidence supporting the use of anti-inflammatory medications (as opposed to surgery or CPAP) as the initial therapy in mild-to-moderate OSA linked to ATH. Given this fact, we would welcome an update of the existing authoritative literature review on this topic.[78] The literature supporting a beneficial effect on SDB of treating rhinitis/rhinosinusitis in adults also continues to grow, and hopefully will command attention from authoritative bodies in the not-too-distant future.

The members of the Work Group on Rhinitis and Sleep-disordered Breathing hope that this survey and literature review will help invigorate the research agenda linking SDB/OSA with upper airway inflammatory conditions, and will encourage a more integrated clinical approach to evaluating and treating SDB in patients with rhinitis and/or ATH. Allergists cannot afford to overlook OSA in adults or children, with or without obvious rhinitis, given its profound implications. Proper management for both children and adults should include coordination with otorhinolaryngology, sleep, and behavioral professionals. It is clear that the area of sleep medicine is an appropriate extension of the scope-of-practice of allergists, and as such should be considered for inclusion in fellowship training curricula.

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