The linkage of allergic rhinitis and obstructive sleep apnea

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Summary

Rhinitis can be divided into allergic and non-allergic rhinitis. Rhinitis, particularly allergic rhinitis, has been shown to be associated with obstructive sleep apnea; a condition characterized by repetitive upper airway obstruction during sleep. Allergic rhinitis increases the risk of developing obstructive sleep apnea by two major mechanisms: 1) increase in airway resistance due to higher nasal resistance and 2) reduction in pharyngeal diameter from mouth breathing that moves the mandible inferiorly. Other inflammatory mediators including histamine, CysLTs, IL 1β and IL-4 found in high levels in allergic rhinitis, have also been shown to worsen sleep quality in obstructive sleep apnea. Prior studies have shown that treatment of allergic rhinitis, particularly when intranasal steroid are used, improved obstructive sleep apnea. Leukotriene receptor antagonists were also associated with positive results on obstructive sleep apnea in adult patients with concomitant allergic rhinitis but current data are limited in the case of children. ***(Asian Pac J Allergy Immunol 2014;32:276-86)***

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Introduction

Rhinitis is characterized by several symptoms including congestion, rhinorrhea, sneezing, and itching.[1] Rhinitis is divided into two categories; allergic and non-allergic rhinitis. Allergic rhinitis results from inhalation of allergens causing production of immunoglobulin (Ig)E antibodies binding to mast cells' IgE receptors in the nasal mucosa and to basophils in the blood. As a result, mast cells release chemical mediators and cytokines that lead to nasal mucosa inflammation.[2] Allergic rhinitis is characterized by early-phase and late-phase responses. Each type of response is characterized by sneezing, congestion, and rhinorrhea, but the congestion symptom is more prominent in the late phase response.[1] Allergic rhinitis is classified as "intermittent" and "persistent" according to the 2001 Allergic Rhinitis and its Impact on Asthma (ARIA) classification.[3] Allergic rhinitis affects 1.4 billion people worldwide and its prevalence is increasing.[4] In the Asia-Pacific region, allergic rhinitis affects approximately 9% of the population, against 14% in the United States and 7% in latin America.[6] Noteworthy, the prevalence of allergic rhinitis in Thai adults vary from 20% to more than 50% with a conservative estimate of 13 million people afflicted.[7-10] The prevalence of allergic rhinitis in Thai children increased dramatically from 17.9% according to a 1990 survey[11] to 44.2% according to the 2002 ISAAC phase I study.[7] Reported risk factors for allergic rhinitis include family history of atopy, serum IgE >100 IU/mL before age 6 years, higher socioeconomic class, and the report of a positive allergy skin prick test (SPT).[1] Typical symptoms of allergic rhinitis include sneezing, rhinorrhea, postnasal drip, nasal obstruction, and itching.[12]

Non-allergic rhinitis, on the other hand, is characterized by non-IgE-dependent events associated with periodic or perennial symptoms of rhinitis including infectious rhinitis, vasomotor rhinitis, and the non-allergic rhinitis with eosinophilia syndrome (NARES).[1]

Obstructive sleep apnea (OSA) is characterized by repetitive complete (apnea), partial (hypopnea)

upper airway obstruction, or respiratory effort-related arousal (RERA) (Figure 1) during sleep. These events typically result in oxygen desaturation and/or arousals during sleep.[13] The combination of the number of apnea and hypopnea per hour of sleep is called apnea hypopnea index (AHI). Both AHI and RERA indexes are used in combination to estimate the respiratory disturbance index (RDI). Diagnosis of OSA is defined by (1) AHI or RDI ≥ 5 plus symptoms related to OSA or comorbidities known to be related to OSA including hypertension, mood disorders, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus or (2) AHI or RDI ≥ 15.[13] Using AHI ≥5 plus symptoms of excessive daytime sleepiness as diagnostic criteria, OSA is commonly reported in approximately 4% of male cases and 2% of female cases. Much higher prevalence was observed when only AHI ≥ 5 events per hour was used as the criteria, with reported prevalence as high as 24% in males and 9% in females.[14] Similar prevalences are commonly observed for subjects in Asian countries. For instance, Niruntarat et al. reported a prevalence of AHI ≥5 plus symptoms of excessive daytime sleepiness and AHI ≥5 to be 15.4% and 4.8% in Thai males; respectively and 6.3% and 1.9% in Thai females, respectively.[15] Risk factors for OSA include increased neck size (> 17 inches in male and >16 inches in female), narrowing of the upper airway, craniofacial abnormalities (i.e. retrognathia, micrognathia), endocrinologic disorders (i.e. acromegaly, hypothyroid), neurologic disorder (i.e. stroke, neuromuscular disorder), nasal obstruction, smoking, alcohol use, obesity, positive family history, end stage renal disease, congestive heart failure, post-menopausal stage and hypertension (more significantly in resistant hypertension)[REF]. OSA recently received attention due to its association with many cardiovascular diseases including hypertension,[16] coronary artery disease,[17] stroke,[18] cardiac arrhythmia,[19] congestive heart failure,[20] pulmonary arterial hypertension,[21] and insulin resistance.[22]

Relationships between allergic rhinitis and obstructive sleep apnea

Daytime sleepiness, fatigue, and headaches are also observed in patients suffering from allergic rhinitis. There are several explanations. Firstly,

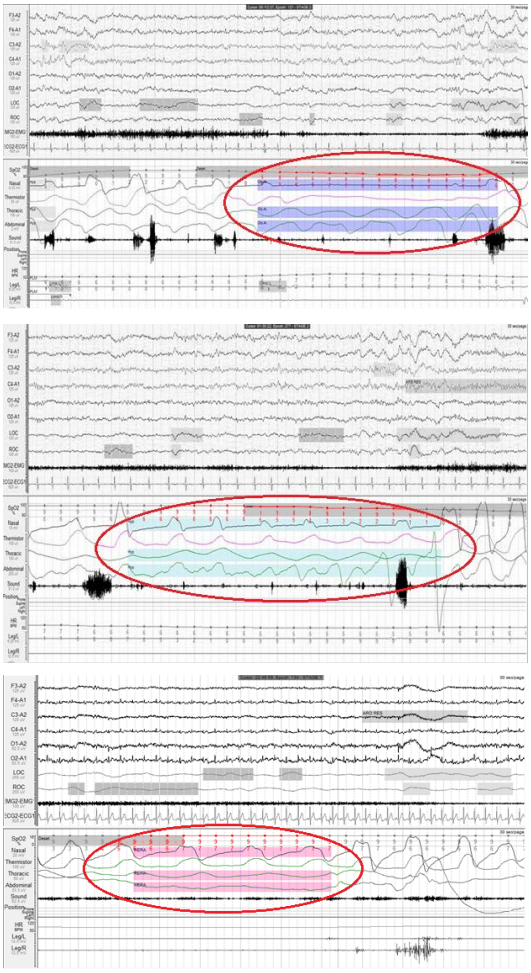

Figure 1. This 30-second epoch shows different obstructive events in red circle including 1.1 obstructive apnea in which there is a 90% reduction in the flow monitored with thermistor monitoring lasting at least 10 seconds with continued respiratory effort 1.2 hypopnea in which there is at least 30% reduction in the flow monitored with nasal pressure monitoring lasting at least 10 seconds associated with reduction in ≥ 3% oxygen desaturation or arousal 1.3-respiratory effort-related arousal (RERA) in which there is a sequence of breaths lasting ≥ 10 seconds associated with increasing respiratory effort or flattening of inspiratory portion of the nasal pressure monitoring associated with arousal F3-A2, left frontal EEG; F4-A1, right frontal EEG; C3-A2, left central EEG; C4-A1, right central EEG; O1-A2, left occipital EEG; O2-A1, right occipital EEG; LOC, left eye electro-occulography; ROC, right eye electrooccuIography; EMG2-EMG1, chin EMG; ECG2-ECG1, electrocardiographic leads; SpO2, oxygen saturation (%); Nasal, nasal pressure monitoring; Thermister, thermister monitoring; Thoracic, thoracic excursion; Abdominal, abdominal excursion; Sound, snoring; Position, position sensor; HR, heart rate; LegL, left anterior tibialis surface EMG; LegR, right anterior tibialis surface EMG [61]

symptoms of allergic rhinitis, particularly rhinorrhea and congestion, can contribute to poor quality sleep and hence fatigue accumulation.[23] Secondly, several inflammatory mediators were reported to be associated with poor sleep including histamine, a known mediator regulating the sleep-wake cycle, arousal, cognition, and memory.[24] CysLTs is another mediator attracting inflammatory cells into nasal tissue perpetuating inflammatory cascade leading to sleep disturbance.[25-27] IL 1β and IL-4 enhancing cytokines are known to be associated with a lower quality of sleep.[28,29] Thirdly, OSA which can cause frequent arousals following obstructive events have been postulated as one mechanism causing daytime sleepiness. Alternatively, obstructive sleep apnea has also been shown to be associated with increased IL-1, IL-6, and tumor necrosis factor (TNF). These inflammatory cytokines may promote T helper type 2 (Th2) cell phenotypes that in turn can cause inflammation leading to nasal congestion.[30]

Pathogenesis of allergic rhinitis and obstructive sleep apnea (Figure 2)

Previous studies have demonstrated that nasal congestion due to allergy was associated with an 1.8-fold increase in the risk of developing moderate to severe OSA, although the relationship between airflow reduction and breathing disorder during sleep was not linear.[31] Another study has shown that nasal obstruction can be an independent risk factor for OSA (defined by AHI ≥15 events per hour in this study). For instance, using posterior rhinomanometry to measure nasal resistance in consecutive snorers, the authors of this study demonstrated that the group of patients with OSA had a higher nasal resistance than the snorers

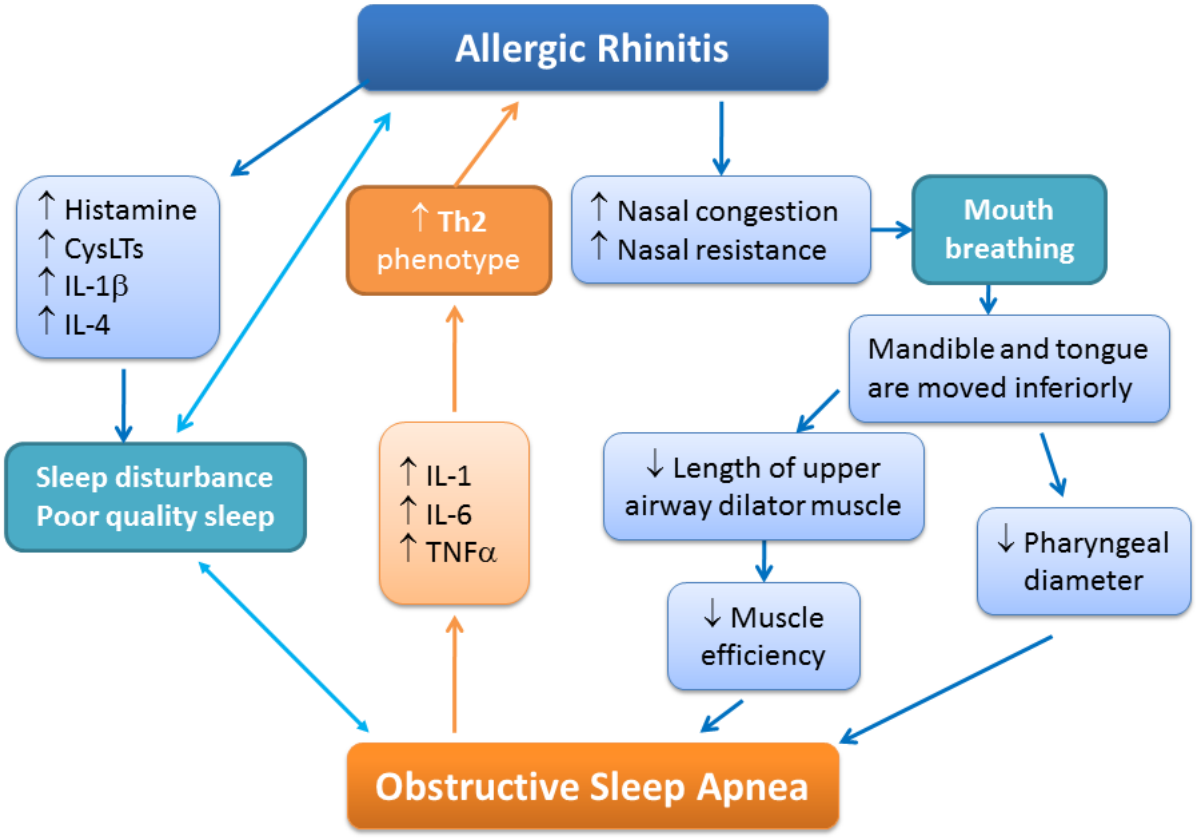

Figure 2. If there is an increase in resistance of upstream segment (Rus) such as that in increase nasal resistance, there will be reduction in maximal velocity (Vmax) through the collapsible tube which will promote increase in airway collapse

without OSA.[32] Similarly, OSA patients were found to have higher congestion factors than non-OSA patients in an acoustic rhinometry study.[33] A certain number of non-mutually exclusive mechanisms explaining the associations between allergic rhinitis and OSA are described thereafter:

1. Increased airway resistance- Although the primary pathological obstructive sites for OSA are located at either the velopharyngeal or retropalatal segments of the upper airway,[34] nasal resistance has also been shown to contribute up to 50% of the upper airway resistance. The Starling resistor model, describing patterns of air-flow through the collapsible tube, recognizes four important determinants of air-flow: pressure upstream (Pus), pressure downstream (Pds), pressure surrounding the tube (Pcrit), and resistance of upstream segment (Rus). The maximal velocity (Vmax) of air is proportional to Pus-Pcrit and is inversely proportional to Rus (Vmax=(Pus-Pcrit)/Rus).[35] When there is an increase in nasal resistance, there is an increase in pressure differential between intraluminal space (negative pressure) and the atmosphere (positive pressure) which induces airway collapse. Although the nasal cavity is relatively rigid, the higher nasal resistance is accompanied by an increase in the Rus that consequently decreases the air-flow through the collapsible tube; the pharynx (figure 3).

2. Mouth breathing- When the mouth is opened, the mandible moves downwards, further displacing the tongue in that direction. The displacement of the tongue is associated with a reduction in the pharyngeal diameter[36] and a shortening of the upper-airway dilator muscles, reducing their efficiency.[37] Mouth breathing is thus mechanically associated with an increase in air-flow resistance. Moreover, impaired nasal reflexes coupled with mouth breathing may further increase the risks for OSA, as minute ventilation, mainly performed through nasal breathing, is then reduced.[36] For instance, prolonged mouth breathing associated with nasal obstruction has been shown to cause long face syndrome in children.[38] The passive tension of the soft tissue of the face and the neck causes the mandible to grow more caudally than anteriorly in turn increasing the risks of OSA in this population.[39]

While the relationship between nasal obstruction and OSA pathogenesis has been mostly investigated and demonstrated in the context of allergic rhinitis, non-allergic rhinitis has also been shown to be a risk factor for high AHI.[40]

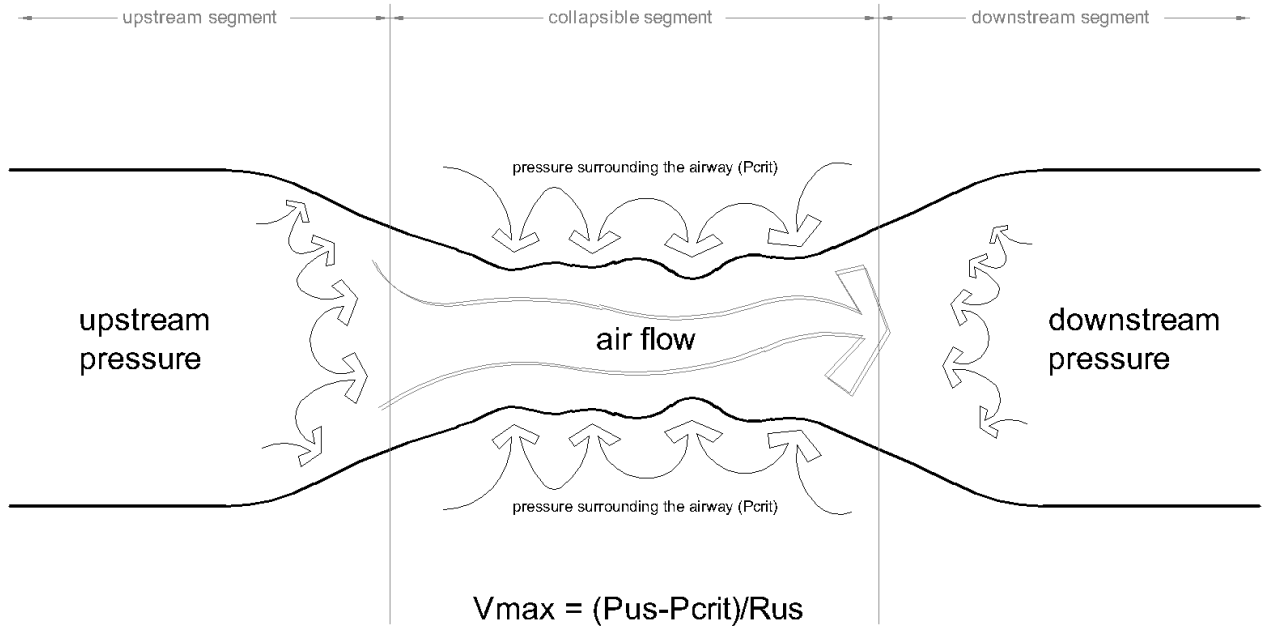

Figure 3. This figure summarizes linkage of allergic rhinitis and obstructive sleep apnea

How allergic rhinitis treatment affects obstructive sleep apnea

The effects of three groups of medication were studied to assess how allergic rhinitis treatment affects obstructive sleep apnea. These includeintranasal corticosteroid, Leukotriene receptor antagonist, and topical nasal decongestion; noteworthy, relevant data is limited as most of the studies assessing treatments effects were not conducted in a randomized-double blinded placebo controlled fashion.

1. Intranasal corticosteroids

Current evidence demonstrated that intranasal corticosteroids are the most effective treatment for allergic rhinitis.[1] Similarly, it is by far the allergic rhinitis treatment that yielded the most beneficial effect on OSA. There was a total of 5 studies focusing on the effect of intranasal corticosteroid on obstructive sleep apnea severity using AHI. Three out of five studies yielded positive results.

A randomized, placebo controlled, crossover designed study demonstrated the effect of the intranasal corticosteroid fluticasone propionate in 23 snorers and their associated rhinitis (13 apneic subjects with AHI≥10 and 10 non-apneic subjects with AHI<10). After a four-week treatment period, in the total population, significantly lower AHI was observed following treatment with fluticasone propionate compared to placebo (11.9 (22.6) vs 20 (26.3)(median (quartile range)); p <0.05) and similar findings were also observed in the apneic group (23.3 (21.3) vs 30.3 (31.9)(median (quartile range)); p <0.05). However, there were no significant differences in oxygen saturation parameters, snoring noise, or sleep quality.[41]

A recent study was conducted to assess the effects of another intranasal corticosteroid, mometasone, administered twice daily at 200 µg for a period of 10-12 weeks in OSA patients both with and without allergic rhinitis. A total of 21 non-allergic rhinitis and 34 allergic rhinitis subjects were enrolled in the study. Polysomnography, sleep quality, level of daytime alertness were assessed and a nasal biopsy for immunocytochemistry (to identify phenotype tissue inflammation) was performed before and after the treatment with intranasal corticosteroid. The study did not demonstrate improvement in overall AHI nor AHI in supine position. However, when a comparison was made between the change in AHI in supine position post-treatment in allergic and non-allergic subjects, stronger reduction in AHI was observed in the allergic group (11.0±20.6 vs 3.3±15; p =0.01). Significant improvement in nadir oxygen saturation was also observed only in the allergic group after treatment with intranasal corticosteroid. The Epworth Sleepiness Scale (ESS) Score was also higher in the allergic group after treatment. Reduction in (EG2) eosinophils was observed at all three biopsy sites (inferior nasal turbinate, nasopharynx, uvula) in the allergic group and only at the nasopharynx site in the non-allergic group. Reduction in CD4 lymphocyte was also observed at all three biopsy sites in the allergic group and only at the inferior nasal turbinate in the non-allergic group. The results of this study therefore suggest the positive effects of intranasal corticosteroid administration on OSA in patients with concomitant allergic rhinitis.[42]

A previous pilot study had evaluated the efficacy of mometasone furoate nasal spray (200 µg) on nasal symptoms, nasal patency, sleep variables, quality of life, and daytime functioning in perennial AR (PAR) and concomitant rhinitis-disturbed sleep (RDS). This double-blind four-week study enrolled patients with perennial allergic rhinitis and rhinitis disturbed sleep. Thirty adults (20 in mometasone group and 10 in placebo group) were included in the study. No difference in AHI was observed between the two groups. However, significant improvement in nasal symptoms, sleepiness using ESS, and impairment in daily activities was observed in the mometasone group. While the majority of the subjects included in this study did not have OSA, mean baseline AHI was 2.57 and 6.39 in mometasone group and placebo group, respectively.[43]

Another randomized, double-blinded, and placebo-controlled study was conducted in moderate to severe OSA (AHI>15) patients with allergic rhinitis based on allergic rhinitis related symptoms including nasal discharge, nasal itching, sneezing, and nasal obstruction plus positive specific IgE test. The study compared four study groups: mometasone furoate spray and desloratadine, mometasone furoate spray and placebo tablet, placebo spray and desloratadine tablet, placebo spray and placebo tablet, with eighty subjects assigned to one of the four treatment groups. After six weeks of randomization, follow-up on clinical symptoms and polysomnography were performed. AHI, oxygen saturation <90%, and ESS scores were improved in the group that received mometasone furoate regardless of desloratadine administration.[44]

Further evidence supporting the effectiveness of intranasal steroid for OSA treatment was found in a pediatric population.[45-47] Intranasal steroid is believed to improve OSA by means of reducing inspiratory upper airway resistance at the nasal, adenoidal, or tonsillar levels.[46] Significant reductions in adenoid size using rhinoscopy were observed in a study conducted in patients between five to 11 years of age, exhibiting chronic obstructive nasal symptoms that had adenoid enlargement. The study was conducted as an eight-week, double-blind, placebo-controlled crossover study using aqueous nasal beclomethasone (total 336 µg/day). The crossover was conducted at four weeks. Significant reduction in adenoid size and improvement in nasal airway obstructive symptoms were observed at four weeks in the nasal beclomethasone group. At eight weeks, both beclomethasone group and placebo group demonstrated improvement which was believed to be resulting from active drug carryover effect in the placebo group.[48]

In a six-week randomized, triple-blind, placebo controlled, parallel-group study using nasal fluticasone propionate in 25 children between one to 10 years of age with OSA, there was a significant reduction in the mixed/obstructive apnea/hypopnea index from 10.7 ± 2.6 to 5.8 ± 2.2 in the fluticasone group but an increase from 10.9 ± 2.3 to 13.1 ± 3.6 in the placebo group (p = 0.04). The Oxygen desaturation index was also significantly improved in the fluticasone group. However, this study did not demonstrate significant reduction in tonsil or adenoid size following treatment. The authors concluded that the shorter duration of the study, the use of lateral neck radiographs to measure the adenoid size instead of direct visualization from the rhinoscopy as well as small sample size may have resulted in non-significant reduction in adenoid size in the fluticasone group.[45]

A reduction in IL-6 released from adenoid tissue was observed in children treated with fluticasone furoate nasal spray prior to undergoing adenotonsilectomy for OSA treatment.[46] However, in the unselected group of OSA patients, nasal steroid did not appear to provide benefit in terms of unwanted nasal side effects or CPAP compliance. [49]

Another study was conducted on 63 patients suffering from moderate to severe OSA syndrome (AHI>10 events/hour) randomly distributed in treatment groups receiving either fluticasone propionate nasal spray or placebo for 10 days prior to and during the first four weeks of CPAP treatment. Despite a difference in mean hours of CPAP usage between the fluticasone propionate nasal spray group and the placebo group (4.3 hours vs 4 hours; respectively), the difference was not statistically significant (p =0.52). After four weeks of CPAP usage, nasal symptoms were similar in both groups according to the score determined from the nasal symptom questionnaire (p =1). Based on current evidence, the American Academy of Sleep Medicine, consider intranasal steroid as a useful adjunct to primary therapies for OSA treatment in patients with concurrent rhinitis.[50,51]

Despite the significance of the studies described, there are a number of limitations (Table 1) that need to be addressed in the future. For instance, studies enrolling more homogeneous OSA severity, in particular less severe groups with concurrent allergic rhinitis are needed. Current evidence suggest that these subgroups may receive the most benefit from intranasal corticosteroids.

2. Leukotriene receptor antagonist

Leukotriene receptor antagonist is one of the commonly used treatments for allergic rhinitis. Interestingly, prior investigations revealed that the cloned human cysteinyl leukotriene receptor 1 and 2 were more abundant in tonsillar tissues of children with OSA when compared to children with recurrent throat infection.[52] There were a total of 3 studies investigating the effects of Leukotriene receptor antagonists on obstructive sleep apnea severity using AHI, mostly in children. Two out of three studies yielded positive results.

Prior studies in pediatric OSA revealed improvement in OSA after the use of leukotriene receptor antagonist. In a study of children with mild OSA defined by AHI >1 but< 5 events per hour, the use of 16 week-open-label treatment with montelukast improved obstructive AHI from 3.0±0.22 to 2.0±0.3 (p =0.017) as well as induced a significant reduction in the obstructive apneic index, arousal index, adenoid size, and significant increase in %REM sleep. [53] The placebo group did not show any improvement.

Another randomized-placebo-controlled trial using montelukast for 12 weeks was conducted in children with non-severe OSA defined by AHI<10 events per hour. The authors of the study demonstrated that montelukast improved the obstructive apnea index (OAI) from 3.9±1.6 to 1.7±1.0 (p <0.01). While obstructive AHI was also improved, no significant differences with the placebo

Table 1. Effect of intranasal steroids on obstructive sleep apnea treatment*

Authors, Year of publication	Medication/ intervention	Population	Age	Study design	Duration	Criteria for OSA enrollment	Results
Brouillette RT, et al, 2001 [45]	Fluticasone propionate vs placebo	25 children with signs or symptoms of OSA with adenoid hypertrophy or tonsillar hypertrophy and mixed/obstructive AHI> 1 on PSG (13 subjects in study group and 12 subjects in control group)	4.2±0.7* (study group) 3.4±0.3* (placebo group) *mean±SD	A triple-blind, placebo controlled, parallel-group study	6 weeks	Mixed/obstructive AHI> 1	Significant reduction in mixed/obstructive AHI and oxygen desaturation index in fluticasone group
Kiely JL, et al, 2004 [41]	Fluticasone propionate vs placebo	23 snorers and associated rhinitis (OSA and non-OSA)	46 (17)* (OSA group) 37.5 (27)* (non-OSA group) *median (quartile range)	A randomized, placebo controlled, crossover study	4 weeks	AHI $\geq$ 10	Significant reduction in AHI, no significant improvement in oxygen saturation parameters, snoring noise, or sleep quality in fluticasone group
Meltzer EO, et al, 2010 [43]	Mometasone furoate vs placebo	Perennial AR and concomitant rhinitis-disturbed sleep (RDS) (20 subjects in study group and 10 subjects in placebo group)	34.6 (21-54)* (study group) 34.4 (22-46)* (placebo group) *mean (range)	A pilot, double-blind study	4 weeks	N/A	No significant reduction in AHI, significant improvement in nasal symptoms, ESS, impairment in daily activities in mometasone group
Lavigne F, et al, 2013 [42]	Mometasone	Mild to moderate OSA with AR (34 subjects) and without AR (21 subjects)	44.8 (9.3)* (OSA with AR) 48 (8.7)* (OSA without AR) *mean (SEM)	A prospective cohort study	10-12 weeks	AHI = 10–40	No significant reduction in AHI, but more reduction AHI was observed in AR group, ESS and nadir oxygen desaturation were improved only in AR group
Acar M, et al, 2013 [44]	Mometasone furoate spray and desloratadine, mometasone furoate spray and placebo tablet, placebo spray and desloratadine tablet, placebo spray and placebo tablet	Moderate to severe OSA with AR (80 subjects were divided into the four treatment group)	Age range 30-50	A randomized, double-blinded, and placebo-controlled study	6 weeks	AHI>15	Significant improvement in AHI, oxygen saturation <90%, and ESS scores in mometasone furoate group regardless of receiving desloratadine or not

*Table only included studies with follow up polysomnography

Table 2. Effect of Leukotriene receptor antagonist on obstructive sleep apnea treatment*

Authors, Year of publication	Medication/ intervention	Population	Age	Study design	Duration	Criteria for OSA enrollment	Results
Goldbart AD, et al, 2005 [53]	Montelukast vs control	Habitual snoring children with mild sleep-disordered breathing (24 subjects in study group and 16 subjects in control group)	5.39±2.0* (study group) 5.7±1.8* (control group) *mean±SD	An open-label intervention study	16 weeks	AHI>1,<5	Significant reduction in obstructive AHI, obstructive apnea index, arousal index, adenoid size, significant increase in %REM sleep in montelukast group
Kheirandish L1, et al, 2006 [55]	Montelukast and intranasal budesonide vs control	Children with residual mild OSA after tonsillectomy and adenoidectomy (22 subjects in study group and 14 subjects in control group)	6.3±1.3* (study group) 6.5±1.8* (control group) *mean±SD	An open-label intervention study	12 weeks	AHI>1, ≤5	Significant reduction in obstructive AHI, nadir oxygen saturation, respiratory arousal index in montelukast and intranasal budesonide group
Goldbart AD, et al, 2012 [54]	Montelukast vs placebo	Snoring children with non-severe OSA (23 subjects in study group and 23 subjects in control group)	4.8±2.0*(study group) 4.7±2.3*(control group) *mean±SD	A randomized-double-blinded-placebo-controlled trial	12 weeks	AHI<10	No significant reduction in AHI, but significant reduction in obstructive apnea index, symptoms, adenoid size in montelukast group

*The table only includes studies with follow up polysomnography

group was observed (6.0±3.22 to 3.6±2.3 (p =0.07)).[54]

Another study using montelukast in conjunction with intranasal budesonide in children with residual mild OSA after tonsillectomy and adenoidectomy (AHI>1 but ≤5 events per hour) showed that obstructive AHI improved from 3.9±1.2 to 0.3±0.3 (p = 0.001). There were also significant improvement in nadir oxygen saturation and respiratory arousal index. No improvement was observed in the non-treatment group.[55]

Based on current evidence, leukotriene receptor antagonists may be considered for treatment of mild OSA in pediatric population either in naïve group or as a rescuer treatment after tonsillectomy and adenoidectomy (Table 2). However, further studies on criteria for patient selection, duration of treatment, and potential combination with other treatment is needed. [56]

3. Topical nasal decongestion

Topical nasal decongestant, an α-adrenergic agonist, was listed as a treatment for allergic rhinitis that can reduce nasal congestion. However, a number of side-effects have been noted. For instance, long term administration of nasal decongestant can result in insomnia, irritability, palpitations, and risk for the development of rhinitis. As a consequence, nasal decongestant is currently only recommended to be used as a short-term treatment. [1] A total of four studies investigating the effects of topical nasal decongestion on obstructive sleep apnea severity using AHI was found in the literature. Only one out of four studies yielded positive results.

In a study conducted on 10 subjects with variable degree of OSA severity, six subjects had symptoms and clinical evidence of chronic nasal obstruction which, in some of the subjects, was associated with markedly elevated nasal resistance. The effects of

Table 3. Effect of topical nasal decongestion on obstructive sleep apnea treatment*

Authors, Year of publication	Medication/ intervention	Population	Age	Study design	Duration	Criteria for OSA enrollment	Results
Kerr P, et al, 1992 [57]	Topical nasal oxymetazolone vs placebo (topical normal saline)	10 subjects with variable OSA severity with and without symptoms of chronic nasal congestion	51 (29-68)* *mean (range)	A randomized placebo-controlled study	3 nights (night 1-acclimatization, night 2 and night 3-study night (receiving topical nasal oxymetazolone or placebo in random order)	Not clearly defined	No significant reduction in AHI, but significant improvement in sleep quality, and mean drop in nasal resistance in topical nasal oxymetazolone group
Braver HM, et al, 1994 [60]	Oxymetazoline nasal spray, side sleeping, and combination treatment	20 asymptomatic male snorers	42±2.6* *mean±SD	A randomized study	4 nights (night 1 -control; the other 3 nights were randomly assigned to nasal decongestant, side sleeping, and a combination of the two)	N/A	No significant reduction in AHI during oxymetazoline night, but significant reduction in AHI during the side sleeping night, and combination treatment night
McLean HA, et al, 2005 [59]	Topical nasal xylometazoline and external dilator strip	10 OSA syndrome with significant nasal obstruction and a normal retroglossal airway dimension	46±5 (18–63)* *mean±SD (range)	A randomized single blind placebo- and sham-controlled crossover study of treatment	One night on each treatment and crossover	OSA symptoms plus AHI or RDI ≥5	Significant reduction in AHI, nasal resistance , the oral fraction of ventilation during sleep, and improvement in sleep architecture on the treatment night
Clarenbach CF, et al, 2008 [58]	Topical xylometazoline vs placebo (topical sodium chloride solution)	12 subjects with OSA and excessive daytime sleepiness (ESS>8) plus chronic nasal congestion	49.1±11.1* *mean±SD	A randomized double-blind, placebo-controlled, cross-over block-design study	3 weeks (1-week of topical xylometazoline and 1-week of topical sodium chloride solution with 1 week washout period)	AHI>10	No significant reduction in AHI, sleep quality, sleep architecture, ESS, but significant increase in nasal conductance in topical xylometazoline group

*The table only includes studies with follow up polysomnography

topical normal saline (placebo) were compared to the effects of topical nasal oxymetazolone (treatment) after one night of application. Although topical nasal oxymetazolone was associated with a subjective improvement in sleep quality and mean drop in nasal resistance of 73% (P <0.001), there was no significant improvement in sleep architecture, nocturnal oxygenation, or the amount of apnea experienced by patients. The most significant improvement was a reduction in arousal index from 52.4 ± 12.4 on placebo to 43.7 ± 10.2 on treatment (P <0.04).[57]

Another study, compared the effects of one week of topical xylometazoline and one week of topical sodium chloride solution application with a one week washout period using a randomized double-blind, placebo-controlled, cross-over block-design. In the study OSA was defined as complaint of excessive daytime sleepiness, an ESS Score >8, and AHI >10 events per hour plus chronic nasal congestion defined by a complaint of impaired nasal breathing that interfered with subjective sleep quality on at least three nights per week during at least the last 3 months. The authors found that AHI

was similar in both groups (29.3 ± 32.5 events/hour vs 33.2 ± 32.8 events/hour; P = NS). However, 30–210 min after application of xylometazoline, at the time of the maximal pharmacologic effect, AHI was significantly reduced when compared to placebo (27.3 ± 30.5 vs 33.2 ± 33.9; $P < 0.01$).[58] The results suggested that the benefit of topical decongestant on OSA treatment appeared to be only transient. Modest improvements in AHI were only observed when topical decongestion was used in combination with other treatments such as a nasal external dilator strip[59] or positional therapy.[60]

Considering the limited evidence supporting the effectiveness of topical nasal decongestant on OSA treatment (Table 3), and the potential side-effects associated with its use, it is not currently recommended for OSA treatment.[50, 51]

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