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Allergic Rhinitis (J Maspero, Section Editor)

Impact and Assessment of Sleep Disturbance in Adults and Children with Allergic Rhinitis

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Abstract

Purpose of Review In this article, we review the impact and the treatment of sleep disturbance caused by allergic rhinitis (AR) in adult and pediatric patients.
Recent Findings Although intranasal corticosteroids (INS) remain the mainstay treatments for AR-induced sleep disturbance, allergen immunotherapy (AIT) has been suggested to be effective in altering the course and progression of moderate-to-severe AR that is refractory to pharmacotherapy. MP-AzeFlu is a recently developed formulation containing azelastine, an intranasal antihistamine (INAH), and fluticasone propionate, an INS. MP-AzeFlu has been reported to have a fast onset of action thanks to the effect of the INAH.
Summary AR is one of the most common chronic inflammatory diseases in the USA with symptoms that can severely affect patients' quality of life. Sleep disturbance is a serious consequence of AR-induced symptoms that can lead to daytime somnolence, impaired cognitive functions, and decreased work/school performance. Nasal congestion and rhinorrhea have been suggested to be the primary causes of sleep disturbance in patients with AR. There is a lack of adequate assessment method for AR-induced sleep disturbance and its consequences in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and the Sino-Nasal Outcome Test-22 (SNOT-22). The NIH-developed Patient Reported Outcome Measurement Information System (PROMIS) has measures for these symptoms. Although more research is needed to develop more pediatric-specific questionnaires, PROMIS is a good start. In terms of treatment for AR-induced sleep disturbance, therapy should be aimed at treating the nasal congestion and rhinorrhea caused by AR. INS are the mainstay treatments for moderate-to-severe AR. The newer INS have low systemic

bioavailability and are well tolerated. For adults, fluticasone propionate is an effective treatment. For children from 2 to 4 years old, mometasone and fluticasone furoate are recommended. Fluticasone propionate should be used in children age 4 or older. Budesonide is the only category B safety drug as classified by the FDA, making it recommended treatment for pregnant and breastfeeding women.

Introduction

Allergic rhinitis (AR) is defined as inflammation of the nasal mucous membranes mediated by immunoglobulin E (IgE) antibodies [1••, 2••, 3••]. AR is estimated to affect 30 to 60 million Americans, 10–25% of the population worldwide, and up to 40% of children [1••, 4]. AR commonly presents as nasal congestion, rhinorrhea, postnasal drip, itching of the nose/throat/eyes, conjunctivitis, and headache [1••, 5].

The symptoms of AR can reduce the quality of life (QoL) of both adults and children [1••, 6••]. A recent survey reports that the majority of patients (or whose child) with seasonal allergy symptoms suffer from irritability, fatigue, and sleep disruption due to their symptoms [7]. In adults, AR is associated with sleep disturbance that can cause impaired cognitive function and decreased work performance [1••, 8]. AR has been associated with increased risk of driving accidents due to impaired sleep and the resulting daytime drowsiness [9]. In children, the effect of AR-induced sleep disturbance can manifest as reduced school performance and/or functioning at home [6••]. Furthermore, inadequate sleep can impact the secretion of growth hormone, which can potentially impact growth rate in children [10]. Of the AR-induced symptoms, nasal congestion and rhinorrhea have been suggested to impair sleep the most [4, 11].

Currently, there are questionnaires addressing AR with very few sleep questions. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, which have been updated in 2016 using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology, are commonly used to evaluate and manage AR [1••]. However, ARIA lacks an adequate assessment method for AR-induced sleep disturbance or the consequences of impaired sleep [6••]. The 22-item Sino-Nasal Outcome Test-22 (SNOT-22) is another commonly used questionnaire that does ask some questions about sleep disturbance and its consequences [12]. However, SNOT-22 has only been validated specifically for chronic rhinosinusitis [12]. In Dass et al., the Patient Reported Outcome Measurement Information System (PROMIS) is a self-reporting assessment tool developed by the National Institutes of Health (NIH) [6••]. Although more effort is needed to validate the use of PROMIS in the general population as well as to develop child-specific questionnaires, PROMIS includes measures that can address sleep disturbance and sleep-related impairment [6••].

Since the symptoms of AR, specifically nasal congestion and rhinorrhea, are the causes of sleep disturbance, treatment options should be focused on relieving these symptoms and AR itself. In fact, the use of intranasal corticosteroids has been shown to significantly reduce nasal congestion and daytime somnolence while also improving sleep in AR patients [13]. The three general treatment options for AR are allergen avoidance (if possible), pharmacotherapy, and allergen immunotherapy [2••, 3••]. Additionally, evidenced-based guidelines such as ARIA have been shown to improve treatment outcomes when followed [3••, 5]. In this article, we review the current treatment of allergic rhinitis and its impact on the QoL and sleep of adult and pediatric patients.

Treatment

Allergen avoidance is a general recommendation for the prevention and treatment of AR [3••]. Patients are encouraged (when possible) to avoid the common allergens such as cigarette smoke, pollen, pets, and any allergens known to

trigger their symptoms [3••]. House dust mites (HDM) are also among the most common inhalant allergens [3••]. However, HDM avoidance and reduction have not been shown to provide clear benefits in terms of AR prevention [2••, 3••]. Conversely, nasal saline irrigation has been shown to help reduce symptoms of AR and improve QoL when used alone or as an adjunctive treatment with INS [2••, 14]. Nasal saline solutions are inexpensive, easy to use, and have not been shown to cause any adverse side effects [3••].

There are also many pharmacologic options for AR. The choice of treatment depends on the severity of AR, patient tolerance, preference in terms of adverse effects versus benefits, and considerations for accessibility and cost [2••, 5]. The step-wise approach for AR with sleep disturbance is to first establish the diagnosis of AR, assess and classify the severity of AR using ARIA and/or PROMIS, and treat accordingly. ARIA classifies AR with any sleep disturbance as moderate-severe [5, 6••]. The common pharmacologic treatments for AR include intranasal corticosteroids (INS), oral and intranasal antihistamines (INAH), leukotriene receptor antagonists (LTRAs), and allergen immunotherapy.

Intranasal corticosteroids are considered first-line agents for moderate-to-severe AR, especially when nasal congestion is one of the prominent symptoms [2••, 4, 5]. There are currently two generations of INS [3••]. The first-generation INS have a higher systemic bioavailability (10–50%) than the second-generation INS (< 1% or undetectable) [3••]. The first-generation INS include beclomethasone, budesonide, flunisolide, and triamcinolone. The second-generation INS include ciclesonide, fluticasone furoate, fluticasone propionate, and mometasone.

There is no evidence showing that any INS is superior to others [2••]. As a general class, INS are well tolerated with few adverse effects that include epistaxis, local irritation and discomfort of the nasal mucosa, and bitter taste from the runoff into the throat [2••, 3••]. Proper administration technique can be used to minimize these effects [3••, 15]. There are concerns, however, regarding the systemic side effects of corticosteroids, such as headache, cataract formation, hypothalamic-pituitary-adrenal (HPA) axis suppression, and growth suppression in children [2••, 3••]. These side effects have been associated with a small number of patients, and most are associated with older INS such as betamethasone and dexamethasone [3••]. Numerous studies have shown that the newer INS are not associated with these effects at the recommended doses [2••, 3••]. However, due to the possible adverse effects on growth, the lowest possible dose of the minimally bioavailable INS should be used in children [3••]. Specifically, mometasone furoate, fluticasone propionate, and fluticasone furoate have been studied extensively in children [3••, 5]. These agents have not shown any suppression of the HPA axis or growth [3••, 5]. Therefore, these specific agents are preferred in pediatric patients. Mometasone and fluticasone furoate can be used in children down to the age of 2, while fluticasone propionate should be used in children age 4 or older [2••, 5].

The use of INS for AR during pregnancy and breastfeeding is another special consideration. A 2016 population-based cohort study of over 140,000 pregnant women in Canada shows that INS use during pregnancy was not associated with any major congenital malformations, slow fetal growth, or spontaneous abortions [16, 17]. Triamcinolone, however, has been associated with an

increased risk of respiratory system defects [16]. Although this finding was based on a small number of cases (5 out of 140,000), it is advisable to avoid using triamcinolone for AR during pregnancy [16]. No other agents were associated with any specific findings [16]. Currently, budesonide is the only category B safety drug as classified by the FDA [2••]. Most of the other INS are in category C [2••]. Overall, the recommendation is to start with budesonide in pregnant women who are using INS for the first time. Aside from triamcinolone, all other INS are also safe to treat AR during pregnancy. For lactating women, budesonide is also the preferred INS due to its minimal passage into breast milk [2••].

Fluticasone propionate, budesonide, and triamcinolone are the INS approved by the FDA to be currently available over the counter [18–20]. These are more accessible to patients so they will be focused on more. Table 1 summarizes the main considerations for these medications.

Fluticasone propionate

Standard adult dosage

Two sprays (50 mcg/spray) per nostril once daily or one spray per nostril twice daily as initial treatment (200 mcg/day) may be reduced to one spray per nostril once daily once symptoms are controlled (100 mcg/day). Use of more than 6 months is not recommended unless instructed by health care provider.

Standard pediatric dose

Children 2 to 4 years: use *fluticasone furoate* only: one spray (27.5 mcg/spray) per nostril once daily (55 mcg/day). Use of more than 2 months per year is not recommended unless instructed by health care provider.

Children 4 to 11 years: one spray (50 mcg/spray) per nostril once daily (100 mcg/day). Use of more than 2 months per year is not recommended unless instructed by health care provider.

Children ≥ 12 years and adolescents: use adult dosing.

Contraindications

Hypersensitivity to any component of the formulation.

Main drug interactions

Strong interaction with CYP3A4 inhibitors: may increase serum concentration of fluticasone. Recommendation: avoid combination.

Desmopressin: may increase hyponatremic effect of desmopressin. Recommendation: avoid combination.

Main adverse effects

Concerns for HPA axis suppression with INS that have high systemic bioavailability. The effect may be potentiated if the INS is used concurrently with ritonavir or any strong CYP3A4 inhibitors.

Table 1. Summary of prescription and over-the-counter intranasal corticosteroids for allergic rhinitis in the USA market

OTC intranasal corticosteroids	Adult dosage	Pediatric dosage	Main adverse effects	Special points
Fluticasone furoate	2 sprays/nostril once daily	2–4 years: 1 spray/nostril once daily 4–11 years: 1 spray/nostril once daily ≥ 12 years: use adult dosing	Local irritation, HPA axis suppression, delayed wound healing, immunosuppression, hypersensitivity reaction	• Pediatric use should not exceed 2 months per year • Proper administration technique can minimize local effects. • Withdrawal should be tapered carefully
Fluticasone propionate [OTC]				
Budesonide [OTC]	2 sprays/nostril once daily	6–12 years: 1 spray/nostril once daily ≥ 12 years: use adult dosing		• Category B safety drug. Recommended for AR during pregnancy and breastfeeding • Proper administration technique can minimize local effects. • Withdrawal should be tapered carefully
Triamcinolone [OTC]	2 sprays/nostril once daily	2–6 years: 1 spray/nostril once daily 6–12 years: 1 spray/nostril once daily ≥ 12 years: use adult dosing	Headache, local irritation, HPA axis suppression, delayed wound healing, immunosuppression, hypersensitivity reaction	• Pregnant women should avoid triamcinolone due to possible risk of congenital respiratory system defects • Proper administration technique can minimize local effects. • Withdrawal should be tapered carefully

Delayed wound healing

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, hypotension. Recommendation: discontinue in severe reactions.

Immunosuppression

Local nasal effects: septal perforation, nasal ulceration, epistaxis, localized *Candida albicans* infections. Recommendation: discontinue if septal perforation occurs.

Special points

The local nasal effects can be minimized by using the proper administration technique. The recommended technique is to aim the INS laterally, away from the nasal septum [3••].

Withdrawal and discontinuation of corticosteroids should be done slowly and carefully to avoid possible adrenal insufficiency.

Budesonide

Standard adult dosage

Rx: one spray (32 mcg/spray) per nostril once daily as initial treatment (64 mcg/day); may be increased up to a maximum of four sprays (128 mcg) per nostril once daily if adequate control is not achieved (maximum dose is 256 mcg/day).

OTC: two sprays (32 mcg/spray) per nostril once daily as initial treatment (128 mcg/day); may be reduced to one spray per nostril once daily when symptoms improve (64 mcg/day).

Standard pediatric dose

Children 6 to 12 years: one spray (32 mcg/spray) per nostril once daily (64 mcg/day). May be increased up to a maximum of two sprays (32 mcg/spray) per nostril once daily if symptoms do not improve (maximum 128 mcg/day). Once symptoms improve, reduce to one spray per nostril once daily (64 mcg/day).

Children ≥ 12 years and adolescents: use adult dosing.

Contraindications

Hypersensitivity to any component of the formulation.

Do not use in children < 6 years of age.

Main drug interactions

Strong interaction with CYP3A4 inhibitors: may increase serum concentration of budesonide. Recommendation: monitor therapy.

Desmopressin: may increase hyponatremic effect of Desmopressin. Recommendation: avoid combination.

Ceritinib: budesonide may enhance the hyperglycemic effect of ceritinib. Recommendation: monitor therapy.

Cobicistat: may increase serum concentration of budesonide. Recommendation: consider another INS. If this combination must be used, monitor therapy closely for systemic HPA suppression effects.

Telaprevir: may increase serum concentration of budesonide. Recommendation: consider another INS, unless the risk is outweighed by potential benefits.

Main adverse effects

Concerns for HPA axis suppression with INS that have high systemic bioavailability. The effect may be potentiated if the INS is used concurrently with any strong CYP3A4 inhibitors.

Delayed wound healing.

Immunosuppression

Local nasal effects: epistaxis, pharyngitis, bronchospasm, cough, mucosal irritation.

Special points

The local nasal effects can be minimized by using the proper administration technique. The recommended technique is to aim the INS laterally, away from the nasal septum [3••].

Budesonide is the only category B safety INS as classified by the FDA; thus, it is preferred for the treatment of AR during pregnancy and breastfeeding.

Withdrawal and discontinuation of corticosteroids should be done slowly and carefully to avoid possible adrenal insufficiency.

Triamcinolone

Standard adult dosage

Two sprays (55 mcg/spray) per nostril once daily (maximum dose 220 mcg/day); may be reduced to one spray (55 mcg) per nostril once daily (110 mcg/day). Discontinue therapy if symptoms do not improve within 3 weeks of prescription use or 1 week for over-the-counter use.

Standard pediatric dose

Children 2 to 6 years: one spray (55 mcg) per nostril once daily (maximum total dose 110 mcg/day).

Children 6 to 12 years: one spray (55 mcg/spray) per nostril once daily (110 mcg/day); may be increased to a maximum of two sprays (110 mcg) per nostril once daily if symptoms do not improve (maximum 220 mcg/day). Once symptoms improve, reduce to one spray per nostril once daily (110 mcg/day).

Children ≥ 12 years and adolescents: use adult dosing.

Contraindications

Hypersensitivity to any component of the formulation.

Do not use in children < 2 years of age.

Pregnant women should avoid triamcinolone due to a possible increased risk of congenital respiratory system defects.

Main drug interactions

Ceritinib: corticosteroids may enhance the hyperglycemic effect of ceritinib. Recommendation: monitor therapy.

Desmopressin: may increase hyponatremic effect of desmopressin. Recommendation: avoid combination.

Main adverse effects

Central nervous system: headache (2 to 51%).

Concerns for HPA axis suppression when used at excessive doses.

Delayed wound healing.

Immunosuppression

Local nasal effects: septal perforation, nasal ulceration, epistaxis, localized *Candida albicans* infections. Recommendation: discontinue if septal perforation occurs.

Special points

The local nasal effects can be minimized by using the proper administration technique. The recommended technique is to aim the INS laterally, away from the nasal septum [3••].

Withdrawal and discontinuation of corticosteroids should be done slowly and carefully to avoid possible adrenal insufficiency.

H_1-antihistamines (both oral and intranasal) and leukotriene receptor antagonists (LTRAs) are the other common medications for AR. H_1-antihistamines work to suppress the histamine-mediated symptoms of AR, including itching, sneezing, and rhinorrhea [2••]. However, they are not as effective as INS at treating nasal congestion, the main symptom causing sleep disturbance [2••]. An advantage of H_1-antihistamines is their fast onset of action, which is typically 15 to 30 min [2••]. ARIA suggests that H_1-antihistamines alone should not be used to treat moderate-to-severe AR [1••]. Instead, H_1-antihistamines should be used in adjunct with INS for this purpose [2••]. LTRAs such as montelukast and zafirlukast have similar effects as the H_1-antihistamines [2••, 3••]. LTRAs are particularly more useful in treating AR patients with concomitant asthma, especially exercise-induced or aspirin-exacerbated respiratory diseases [1••, 2••]. However, they should also be combined with INS for moderate-to-severe AR.

Oral H_1-antihistamines (OHAs) have two generations. The first-generation OHAs include diphenhydramine, chlorpheniramine, and hydroxyzine. These older OHAs are more lipid-soluble and, thus, can cross the blood-brain barrier (BBB) more readily [2••]. The first-generation OHAs are known to have sedating effects [2••]. The second-generation OHAs are much less likely to cross the BBB due to their more complex chemical structures [2••]. Besides cetirizine, second-generation OHAs such as loratadine, desloratadine, fexofenadine, and levocetirizine have reduced effects on the central nervous system and are more

well tolerated overall [2••]. Intranasal H_1-antihistamines (INAH) such as azelastine and olopatadine have similar efficacy as OHAs and are also known to cause sedation [2••]. ARIA suggests that the choice of treatment between INS alone, a combination of INS/OHA, or a combination of INS/INAH for moderate-to-severe AR should largely depend on the patient preferences, local availability, and cost/effectiveness [1••].

MP-AzeFlu is a recently developed formulation that contains both azelastine hydrochloride, an INAH, and fluticasone propionate, an INS [4]. This formulation takes advantage of the rapid symptom relief of the INAH and the slower anti-inflammatory effects of the INS [4]. MP-AzeFlu has been reported to have an onset of action at 30 min [4]. This single formulation has been shown to have higher effectiveness and faster relief in patients with more severe AR [2••]. However, the most recent ARIA revision in 2016 suggests that either a combination of an INAH with an INS or an INS alone could be used for treatment of moderate-to-severe AR [1••]. ARIA suggests that more research measuring cost-effectiveness is needed to further justify the use of this new combination [1••]. However, ARIA acknowledges that some patients do prefer MP-AzeFlu due to its rapid onset of action [1••]. Therefore, the choice of treatment will depend largely on patient preferences as well as availability and cost. MP-AzeFlu has been reported to cost about $220–$250 for a 23-g unit containing 137 – 50 mcg/spray.

Lastly, allergen immunotherapy (AIT) is the recommended treatment for moderate-to-severe AR that is unresponsive to pharmacotherapy [2••, 3••, 21]. AIT involves the regular administration of purified allergen extracts [21, 22]. Unlike the pharmacologic treatment, which focuses on relieving the symptoms of AR, AIT is the only treatment that can alter the disease course and progression [21]. Allergic rhinitis and allergy in general involve a T_H2 (humoral) cell response and IgE production [21]. AIT shift this T_H2 response toward a T_H1 (cellular) cell response and regulatory T cell (T_{reg}) response [21]. T_{reg} lymphocytes are also known to have immunosuppressive effects by releasing IL-10 and TGF-β [21]. AIT can be administered as subcutaneous injections (SCIT) or as sublingual drops/tablets (SLIT) [21]. Although there is a lack of standardization across studies in terms of allergens, dose, and administration route, both SCIT and SLIT have been shown to significantly reduce symptoms of AR [21, 22]. SLIT has been indirectly shown to be as effective as topical corticosteroids in treating both adults and children with seasonal AR [21]. There are few studies that directly compare the efficacy of SCIT against SLIT [21]. However, SCIT may be slightly superior to SLIT at treating AR [2••].

A big concern of AIT, especially SCIT, is the risk of severe systemic reaction [21]. SCIT has been associated with severe anaphylactic reaction requiring adrenaline administration in 3.5% of cases (13 studies with 557 patients) [21]. Therefore, SCIT should only be administered in a physician's office, and patients should remain in the office for at least 30 min to be observed for any systemic allergic reaction [21]. SLIT, on the other hand, is well tolerated with much lower risk for severe anaphylactic reactions [21]. Another advantage of SLIT is that only the first SLIT administration needs to be administered in the physician's office. The subsequent treatment can be self-administered at home [21]. The major adverse effects of SLIT include oral mucosa reactions in 40–75% of cases [21]. There have been case reports

of eosinophilic esophagitis (EoE) with grass, mixed tree pollen, and HDM SLIT [23]. A history of EoE is a contraindication for SLIT [23]. Besides severe anaphylactic reaction, another disadvantage of AIT is patient compliance [2••, 21]. Both SLIT and SCIT are recommended to be given continuously for at least 3 years [2••, 21]. In a study in the Netherlands, only 18% of almost 6500 patients completed the 3-year course (23% with SCIT and 7% with SLIT) [21]. Furthermore, the use of SLIT in the USA has been limited due to high cost [2••].

Overall, AIT is a promising treatment for moderate-to-severe AR that is refractory to pharmacologic treatment. SCIT has a better safety profile and can be self-administered at home after the first dose. However, due to their long treatment course, health care providers should encourage their patients to regularly follow-up with them to improve compliance with AIT.

Conclusions

Sleep disturbance caused by symptoms of allergic rhinitis (AR) can seriously impair patients' daily functions. Nasal congestion and rhinorrhea are most likely the causes of sleep disturbance in patients with AR. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and the Sino-Nasal Outcome Test-22 (SNOT-22) are commonly used to assess and manage AR and chronic rhinosinusitis. However, both lack an adequate and specific assessment method for sleep disturbance caused by AR. The NIH-developed Patient Reported Outcome Measurement Information System (PROMIS) includes measures for sleep disturbance and its consequences. Treatment for AR-induced sleep disturbance should be focused on treating AR itself. Intranasal corticosteroids (INS) are the mainstay treatments for moderate-to-severe AR. The newer INS have low systemic bioavailability and are well tolerated. For adults, fluticasone propionate is an effective treatment. For children from 2 to 4 years old, mometasone and fluticasone furoate are recommended. Fluticasone propionate should be used in children age 4 or older. Budesonide is recommended for pregnant and breastfeeding women because it is the only category B safety drug as classified by the FDA.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent
With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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