

Treatment of congestion in upper respiratory diseases

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Abstract: Congestion, as a symptom of upper respiratory tract diseases including seasonal and perennial allergic rhinitis, acute and chronic rhinosinusitis, and nasal polyposis, is principally caused by mucosal inflammation. Though effective pharmacotherapy options exist, no agent is universally efficacious; therapeutic decisions must account for individual patient preferences. Oral H₁-antihistamines, though effective for the common symptoms of allergic rhinitis, have modest decongestant action, as do leukotriene receptor antagonists. Intranasal antihistamines appear to improve congestion better than oral forms. Topical decongestants reduce congestion associated with allergic rhinitis, but local adverse effects make them unsuitable for long-term use. Oral decongestants show some efficacy against congestion in allergic rhinitis and the common cold, and can be combined with oral antihistamines. Intranasal corticosteroids have broad anti-inflammatory activities, are the most potent long-term pharmacologic treatment of congestion associated with allergic rhinitis, and show some congestion relief in rhinosinusitis and nasal polyposis. Immunotherapy and surgery may be used in some cases refractory to pharmacotherapy. Steps in congestion management include (1) diagnosis of the cause(s), (2) patient education and monitoring, (3) avoidance of environmental triggers where possible, (4) pharmacotherapy, and (5) immunotherapy (for patients with allergic rhinitis) or surgery for patients whose condition is otherwise uncontrolled.

Keywords: allergic rhinitis, congestion, obstruction, rhinosinusitis, treatment

Introduction

Congestion, which may be best described as a feeling of blockage, fullness, or restricted airflow, is a primary symptom of common upper respiratory tract disorders, including allergic rhinitis, acute rhinosinusitis, chronic rhinosinusitis, and nasal polyposis. Congestion impacts negatively on patient quality of life by interfering with both sleep and daytime activities. In allergic rhinitis, it is the symptom patients find most bothersome and would like most to prevent.^{1,2} Congestion may also exert secondary effects on the paranasal sinuses, ears, throat, voice, and chest that manifest as irritated throat, headaches, impairment in hearing, reduced ability to smell, worsening of asthma, problematic snoring, and disturbance of sleep.²

The principal underlying cause of nasal congestion in common upper airway disorders in adults is inflammation, which usually manifests as venous engorgement, increased nasal secretions, and tissue swelling/edema that ultimately leads to impaired airflow and the sensation of nasal blockage. Consequently, development of pharmacologic therapies for congestion in these diseases has been guided by the need to target underlying pathophysiologic mechanisms including inflammation

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(ie, anti-inflammatory activity of intranasal corticosteroids) and its manifestations such as venous engorgement (ie, vasoconstrictive action of decongestants). It is important to note that the perception of congestion in chronic rhinosinusitis can also be caused by polyps extruding into the nasal airway, producing a physical obstruction in the nostrils.

The pervasiveness of allergic rhinitis³ and rhinosinusitis^{4,5} has caused congestion to become a highly prevalent problem, even when less common causes are excluded. In addition, the upper airway respiratory diseases in which congestion is a common symptom (ie, allergic rhinitis, nonallergic/vasomotor rhinitis, rhinosinusitis, nasal polyposis, and the common cold) are undertreated due to the lack of efficacy with some current therapies^{6–8} and safety concerns with others.^{6,9,10} Thus, there remains a large unmet clinical need for options for congestion, and further study and more effective therapies are necessary to improve treatment. This review covers treatment considerations for congestion associated with the common upper airway diseases described above. Also presented is a brief overview of treatments for some of the less common rhinopathies, as well as surgical options for congestion due to mechanical abnormalities and treatment-resistant chronic rhinosinusitis.

Treatment considerations

A stepwise approach is recommended for the management and treatment of nasal congestion. The 5 main principles are (1) diagnosis of the cause(s), (2) patient education and monitoring, (3) avoidance of environmental trigger factors where possible, (4) pharmacotherapy, and (5) allergen immunotherapy (only in patients with allergic rhinitis with documented sensitivity to specific allergens) or surgery for patients in whom the condition cannot be controlled with the previous measures.¹¹

Patient education should involve the patient, family members, and any caregivers. Ideally it should begin at the time of diagnosis and continue throughout clinical care. Education of the patient should include an explanation of the condition and a definition of therapeutic goals. The physician should inquire about the patient's concerns and preferences for various interventions and discuss potential side effects of treatment.¹² Effective disease management should include a regular review of the treatment goals and monitoring of patient progress, including treatment adherence.

Once a diagnosis has been established, environmental triggers that may contribute to congestion should be avoided when possible. These triggers include allergens (eg, pollen, dust mites, animal dander, mold spores, cockroach

droppings), irritants (eg, smoke, fumes, strong odors), and infectious agents.¹³ Environmental controls need to be tailored to the individual patient's exposures and sensitivities. Unfortunately, such controls are not always practical, effective, or indicated, and thus supplemental medical treatment is often required.¹ For allergen exposure, environmental adjustments that have demonstrated efficacy include trigger avoidance, low indoor humidity (below 50%), allergen-proof pillows and mattress covers, minimizing carpeting, and minimizing fur-bearing pet contact.^{13,14} Although a high-efficiency particulate air (HEPA) vacuum filter may reduce animal and dust mite allergen exposure, the evidence of its effectiveness in alleviating symptoms is not conclusive. Vacuuming of rugs is not effective in decreasing animal allergens, because it only eliminates superficial areas and does not clean the deeper levels of the rug.¹³ For irritants related to employment, appropriate control measures (eg, fume hoods, positive pressure ventilation, air filtration, self-contained breathing units) should be implemented.

When developing a strategy for the pharmacologic treatment of nasal congestion, a physician should consider a number of factors, including the underlying etiology of the condition, likely pathophysiology and dominant symptom(s). The efficacy and safety of possible drug choices should be weighed against specific patient characteristics such as comorbid airway disorders, age, appropriateness of drug formulations, patient preference, prior and current therapy, and compliance history.¹² In a 2005 survey of 783 allergy medication users conducted by the Gallup Organization, respondents were asked which drug characteristics were most important to them. The most important properties to patients were: specifically targets individual symptoms (86%), fast onset of action (81%), few adverse events (79%), nonhabit forming (77%), and long duration of action (77%).¹⁵

Creating a collaborative partnership with patients and their families will help improve adherence. Clinical decisions should not only be made on the basis of the best available evidence but should also be consistent with patients' expectations, preferences, goals, and capabilities. Patient adherence and compliance may also be affected by access to medications, including issues of product or formulation availability and cost. Important factors in improving patient adherence also include the selection of medications most appropriate to the patient's clinical profile, avoidance of problems associated with past treatment, and appraisal of any new medications' product attributes to determine if they align with the patient's preferences. Patients should be instructed on the correct way

to use medication and encouraged to ask questions. Patient satisfaction with treatment should also be included in the process of follow-up and monitoring.

Medications that have been extensively evaluated in adequately designed clinical trials for the treatment of congestion associated with various upper respiratory disorders include oral and intranasal antihistamines, leukotriene receptor antagonists, oral and intranasal decongestants, and intranasal corticosteroids.^{6,7,11} Other therapies such as intranasal cromones,⁶ topical lysine aspirin,¹⁶ topical anticholinergics,⁶ systemic corticosteroids,¹¹ capsaicin,^{17,18} menthol,¹⁹ and nasal douching⁶ have also been used for treatment of congestion, mostly in patients with rhinitis, but their ability to provide congestion relief has not been unequivocally demonstrated.

In patients with congestion due to allergic rhinitis, immunotherapy may be considered when previous options have proven insufficient to control symptoms. Immunotherapy has demonstrated efficacy against congestion and is the only intervention for allergic rhinitis that alters the natural history of the disease.²⁰

Pharmacologic therapy for congestion

Antihistamines

H₁-antihistamines exert their antiallergic effects by inhibiting the binding of histamine, an important mediator of allergic response, to the H₁ histamine receptor.⁶ First-generation oral H₁-antihistamines, such as chlorpheniramine, diphenhydramine, and triprolidine, are associated with marked sedation, whereas the more recently introduced second-generation oral H₁-antihistamines, including acrivastine, astemizole, azelastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, and terfenadine, have a more favorable benefit-to-risk profile (some of these agents are available only in Europe).^{6,10} Intranasal antihistamines include azelastine, levocabastine, and olopatadine.^{6,10,21}

Although oral and intranasal H₁-antihistamines have demonstrated efficacy against nasal congestion in patients with allergic rhinitis,^{10,22} the magnitude of benefit is relatively modest and less pronounced than that observed with decongestants or intranasal steroids.^{10,23–28} Some improvement in congestion with oral and/or intranasal H₁-antihistamines has also been reported in patients with nonallergic/vasomotor rhinitis,^{29,30} rhinosinusitis,³¹ and nasal polypsis,^{32,33} whereas no effect on congestion was evident in studies of H₁-antihistamines in patients with the common cold.^{34–36} Key features of antihistamines include convenient oral or

intranasal administration (in many cases, once daily), rapid onset of symptom relief, and good overall safety and tolerability profile.

Congestion efficacy in allergic rhinitis

Oral antihistamines

A recent meta-analysis of studies with oral H₁-antihistamines in allergic rhinitis has demonstrated significant improvements in both patient-rated and physician-rated congestion.²² However, compared with their efficacy against other nasal symptoms associated with allergic rhinitis (eg, nasal itching, sneezing, rhinorrhea), oral (and intranasal) H₁-antihistamines appear to be less effective for relief of congestion/obstruction.^{6,10} Nevertheless, in clinical trials with various agents, both oral and intranasal antihistamines have demonstrated some congestion relief in patients with allergic rhinitis.

A placebo-controlled study of patients with seasonal allergic rhinitis reported that oral acrivastine 4 mg twice daily and 8 mg twice daily led to significant reductions in total symptom score, sneezing and runny nose, but the improvements in congestion did not achieve statistical significance.³⁷ In a placebo-controlled trial with terfenadine 60 mg twice daily and astemizole 10 mg once daily in patients with seasonal allergic rhinitis, astemizole showed superior relief of sneezing and runny nose versus both placebo and terfenadine, but the congestion scores with either antihistamine were not superior to placebo.³⁸ Oral azelastine has demonstrated efficacy against nasal symptoms of perennial allergic rhinitis, but the improvement in congestion was only modest and did not achieve statistical significance at either the 1-mg twice daily or the 2-mg twice daily dose level.³⁹ Studies with ebastine 10 mg and 20 mg in seasonal and perennial allergic rhinitis^{40,41} have also demonstrated some congestion relief versus placebo, but the improvement in congestion in patients with perennial allergic rhinitis failed to reach statistical significance with either dose.⁴⁰ Mizolastine therapy in patients with perennial allergic rhinitis also reduced congestion score after 4 weeks of treatment, but the improvement over placebo was not statistically significant.⁴²

Some of the most extensively evaluated second-generation oral H₁-antihistamines in allergic rhinitis include loratadine, fexofenadine, cetirizine, desloratadine, and levocetirizine. In a study of adults with seasonal allergic rhinitis, loratadine was associated with greater improvements in nasal stuffiness score at day 4 and overall versus placebo, although the differences were not statistically significant for either comparison.²⁴ A 4-week trial in adults with perennial allergic rhinitis showed that loratadine 10 mg once daily and

terfenadine 60 mg twice daily both significantly reduced nasal stuffiness compared with placebo.⁴³ A pooled analysis of 3 studies in children with seasonal allergic rhinitis showed that fexofenadine 30 mg twice daily significantly reduced all nasal symptoms versus placebo, including congestion,⁴⁴ and a separate study in adults with seasonal allergic rhinitis reported that fexofenadine 120 mg once daily for 2 weeks significantly reduced nasal congestion score versus placebo.⁴⁵ In a small study of 31 patients with perennial allergic rhinitis, fexofenadine 120 mg once daily and 180 mg once daily both significantly decreased nasal congestion from baseline beginning 1 week after treatment and persisting until the end of 4 weeks of treatment, in contrast to the absence of significant reduction with placebo.⁴⁶ However, fexofenadine is not approved for treatment of perennial allergic rhinitis in either the United States or Europe. A 2-week placebo-controlled trial in adults with seasonal allergic rhinitis demonstrated significant improvements in congestion with both fexofenadine (120 mg once daily and 180 mg once daily) and cetirizine 10 mg once daily, but the magnitudes of improvement were less pronounced than for other nasal symptoms.⁴⁷ In a 4-week study in adults with perennial allergic rhinitis, improvement in congestion with cetirizine 10 mg once daily and 20 mg once daily was also greater than that observed with placebo, although the reductions in other nasal symptoms, most notably postnasal discharge and sneezing, were greater.⁴⁸ In adults with intermittent allergic rhinitis, 2 weeks of therapy with desloratadine 5 mg once daily significantly reduced nasal congestion versus placebo at all time points evaluated.⁴⁹ In patients with perennial allergic rhinitis, desloratadine 5 mg once daily significantly reduced all nasal symptoms with the exception of congestion over the 4-week treatment period.⁵⁰ Treatment of adult patients with seasonal allergic rhinitis with 3 different dosing regimens of levocetirizine (2.5 mg once daily, 5 mg once daily, and 10 mg once daily) for 2 weeks failed to significantly improve nasal congestion versus placebo despite superior efficacy on other nasal symptoms.⁵¹ In adults with persistent allergic rhinitis, therapy with levocetirizine 5 mg once daily was associated with a nonsignificant trend toward greater reduction in nasal congestion versus placebo at weeks 1 or 4, and the reduction achieved statistical significance after 6 months of treatment.⁵²

Intranasal antihistamines

In general, clinical trials with intranasal antihistamines have demonstrated some efficacy against nasal congestion in allergic rhinitis compared with placebo, although no

meta-analyses of studies with different agents have been published to date. Intranasal azelastine twice daily for 2 weeks reduced nasal congestion in adults with seasonal allergic rhinitis significantly more than oral cetirizine 10 mg once daily. In an 8-week study in adults with perennial allergic rhinitis, intranasal azelastine failed to significantly reduce congestion versus placebo, in contrast to a significant reduction in congestion versus placebo reported with the intranasal steroid flunisolide.⁵³ A 6-week trial in adults with seasonal allergic rhinitis showed minimal improvement in congestion-free days with intranasal levocabastine over placebo, whereas a significant improvement in congestion-free days versus placebo was observed with intranasal fluticasone propionate.⁵⁴ A separate 4-week trial in adults with seasonal allergic rhinitis reported inferior all-day congestion relief with intranasal levocabastine compared with mometasone furoate nasal spray.⁵⁵ Intranasal olopatadine therapy for 2 weeks in adults with seasonal allergic rhinitis was associated with significant congestion relief compared with placebo in one study.⁵⁶ But the reduction in congestion reported in a separate trial in adults with seasonal allergic rhinitis did not achieve statistical significance.⁵⁷

Congestion efficacy in nonallergic/vasomotor rhinitis

Only one study evaluated the effect of an oral antihistamine on congestion exclusively in patients with nonallergic rhinitis, although it is difficult to discern its effect because it was given in combination with an intranasal steroid. In that study, the addition of oral loratadine to intranasal flunisolide resulted in greater improvements in sneezing and rhinorrhea compared with flunisolide alone, but did not improve congestion.³⁰ In a population of patients with perennial allergic and nonallergic rhinitis, oral astemizole had a marginal effect on nasal congestion, in contrast to a significant improvement in congestion observed with intranasal steroid beclomethasone dipropionate.⁵⁸

In a 2-week study in patients with vasomotor rhinitis, intranasal azelastine significantly reduced congestion at 15 days, but the improvement reported at 8 days was not statistically significant.⁵⁹ Some improvement of congestion with intranasal azelastine in patients with vasomotor rhinitis was also reported in another trial, although the effect was not consistently significant.²⁹ A trial in patients with allergic and nonallergic disease, including symptoms of nasal obstruction, found no consistent benefit of intranasal levocabastine over placebo on nasal obstruction, and the intranasal steroid beclomethasone dipropionate was shown to be superior to levocabastine for nasal obstruction relief.⁶⁰

Congestion efficacy in rhinosinusitis

Only one study reported the effect of an oral antihistamine on nasal congestion in patients with acute rhinosinusitis. This study demonstrated that, in patients with allergic rhinitis experiencing acute exacerbations of rhinosinusitis, loratadine significantly improved nasal obstruction compared with placebo after 28 days of treatment.³¹

Congestion efficacy in nasal polyposis

The only published study of oral antihistamine efficacy on congestion in nasal polyposis was conducted in patients with residual or recurrent nasal polyposis after ethmoidectomy who were treated with either cetirizine at twice the daily recommended (20 mg) dose or placebo for 3 months.³² The percentage of days with nasal obstruction score ≤ 1 (on a scale from 0 [no discomfort] to 3 [severe discomfort]) at weeks 4 and 8 in the cetirizine and placebo groups was similar, while patients treated with cetirizine had significantly more such days than placebo-treated patients at week 12.³² In the only trial of an intranasal antihistamine in patients with nasal polyps (and perennial allergic rhinitis), postsurgery treatment with azelastine nasal spray (0.14 mg to each nostril twice daily) had no consistent effect on nasal obstruction over a 25-week treatment period.³³

Congestion efficacy in the common cold

In a trial in patients with the common cold, the reduction in congestion after 4 days of treatment with terfenadine 120 mg twice daily for 4 to 5 days was similar to that reported with placebo.³⁴ A separate study in adults with the common cold reported that the combination of an oral antihistamine and decongestant (loratadine and pseudoephedrine) resulted in significant relief of patient-reported nasal stuffiness on days 1 to 5 of treatment compared with placebo,⁶¹ but the effect attributable to the antihistamine could not be differentiated from that of the decongestant. In contrast, 2 other studies in patients with the common cold did not show a significant improvement in congestion with the combination of an antihistamine and a decongestant.^{62,63}

Safety

The use of first-generation antihistamines (eg, diphenhydramine, brompheniramine, chlorpheniramine) is associated with a number of adverse central nervous system (CNS) sedation effects, including somnolence and performance impairment.¹² Other side effects of the older agents include anticholinergic effects, such as dryness of the mouth, urinary retention, and blurred vision.¹² The newer

H₁-antihistamines, including cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, are preferred to older agents because they have similar H₁-receptor inverse agonist activity compared but are consistently less sedating, presumably due to reduced CNS penetration.⁶⁴

In summary, clinical evidence suggests that antihistamines are, at best, a modestly effective therapy for congestion associated with allergic rhinitis. However, their decongestant action is generally insufficient and inferior to that of intranasal steroids. Antihistamines may also provide some congestion relief in nonallergic upper respiratory diseases, although the supporting evidence is limited. From a safety standpoint, second-generation oral antihistamines are preferred over earlier agents because of an improved safety profile, although somnolence and performance impairment have also been reported with some of them.

Leukotriene receptor antagonists

Leukotrienes are contributing mediators of nasal allergic reactions, and their presence in the nose may lead to nasal obstruction.⁶ Therefore, a pharmacologic agent that inhibits the effects of leukotrienes might offer relief of symptomatic nasal congestion. Leukotriene receptor antagonists zafirlukast and montelukast have receptor affinities that are approximately 2 times greater than that of the natural ligand LTD₄,⁶ which may enhance their clinical efficacy. Leukotriene receptor antagonists have demonstrated some efficacy against nasal congestion in allergic rhinitis and rhinosinusitis, although they appear to be inferior to intranasal steroids in this regard.

Congestion efficacy in allergic rhinitis

A meta-analysis of 6 placebo-controlled trials in patients with allergic rhinitis demonstrated that leukotriene receptor antagonists significantly reduce total nasal symptoms versus placebo, but the effect on congestion or other individual symptoms was not reported.⁶⁵ While several small studies have evaluated the efficacy of zafirlukast^{66,67} and zileuton⁶⁸ in patients with allergic rhinitis, montelukast has been the only leukotriene receptor antagonist studied in large trials in these patients. A study in 1302 patients with seasonal allergic rhinitis found that both montelukast and the antihistamine loratadine produced a modest decongestant effect after 2 weeks of treatment, with greater effects on other nasal symptoms.⁶⁹ The combination of loratadine plus montelukast was found to be significantly more effective than either therapy alone for daytime nasal symptoms in patients with seasonal allergic rhinitis, although the effect on congestion was not significantly different

from montelukast alone.⁷⁰ Moinuddin et al reported that the combination of loratadine and montelukast administered for 2 weeks significantly improved peak nasal inspiratory flow in patients with seasonal allergic rhinitis, with the effect comparable to treatment with fexofenadine and pseudoephedrine.⁷¹ In a study of 1992 adults with perennial allergic rhinitis, 6 weeks of treatment with montelukast achieved a significantly greater improvement in all daytime nasal symptoms, including congestion, than placebo, although the study may have been overpowered (Figure 1).⁷²

Several studies have documented that the congestion relief with leukotriene receptor antagonists is inferior to that achieved with intranasal steroids.^{8,73,74} In addition, the combination of leukotriene receptor antagonists and H₁-antihistamines has also been shown to provide significantly less effective congestion relief than intranasal steroids.⁶⁵

Congestion efficacy in nonallergic/vasomotor rhinitis

There are no published reports on the efficacy of leukotriene receptor antagonists for relief of congestion associated with nonallergic/vasomotor rhinitis.

Congestion efficacy in rhinosinusitis and/or nasal polyposis

Antileukotrienes have not been adequately studied for the treatment of congestion associated with rhinosinusitis or nasal polyposis.⁷ In a small study of 40 patients who

underwent surgery for nasal polyps, postoperative therapy with montelukast was significantly less effective than intranasal beclomethasone for congestion relief over 12 months.⁷⁵

Congestion efficacy in the common cold

No studies have been published on the efficacy of leukotriene receptor antagonists for relief of congestion associated with the common cold.

Congestion efficacy in aspirin triad disease

A small retrospective analysis reported the effect of antileukotriene therapy (zarfirlukast or zileuton) for relief of congestion in patients with aspirin triad disease who had persistent chronic rhinosinusitis despite previous paranasal sinus surgery.⁷⁶ Patient self-reports showed significant improvement in congestion and other major and minor symptoms, which was consistent with the findings of endoscopic nasal exams.⁷⁶

Safety

Pediatric studies have demonstrated that montelukast is well-tolerated, with the majority of adverse events, including headache, ear infection, nausea, abdominal pain, and pharyngitis, being mild.⁷⁷ The incidence of these adverse events with montelukast does not appear to be higher than with placebo.⁷⁸ No dose adjustment with montelukast is necessary for patients with renal or mild-to-moderate hepatic dysfunction.⁷⁹

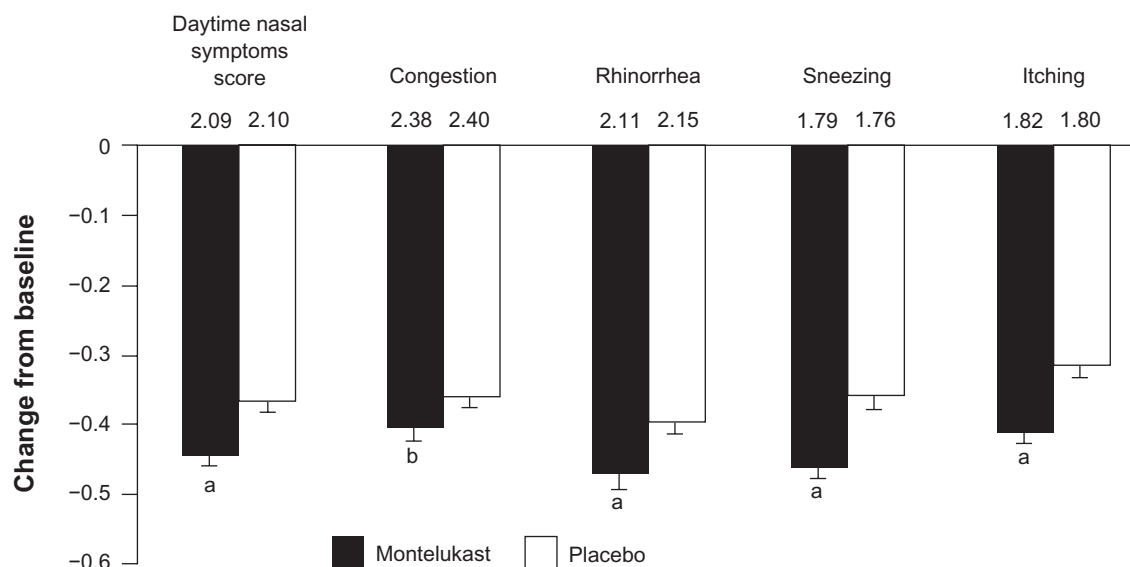


Figure 1 Least squares mean change in the composite daytime nasal symptoms score and its components during a 6-week trial of montelukast versus placebo in patients with perennial allergic rhinitis. Baseline scores are shown above the bars. * $P < 0.001$; ^b $P < 0.05$. Error bars represent SE. Reproduced with permission from Patel P, Philip G, Yang VW, et al Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol*. 2005; 95(6):551–557.⁷² Copyright © 2005 American College of Allergy, Asthma and Immunology.

Recently, the Food and Drug Administration (FDA) published reports of neuropsychiatric events associated with the use of montelukast and other antileukotrienes, including postmarket cases of agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, suicidal thinking and behavior, and tremor. The FDA recommended remaining alert for such events and considering discontinuation of medication if these symptoms develop.⁸⁰ Isolated reports of Churg-Strauss syndrome, a rare systemic vasculitis associated with asthma, have been described in asthma patients treated with montelukast; a causal relationship has not been established.⁸¹

In summary, the leukotriene receptor antagonist montelukast has demonstrated some efficacy against nasal congestion in allergic rhinitis. Its decongestant effects, both alone and in combination with an H₁-antihistamine, are inferior to that observed with intranasal corticosteroids. The congestion efficacy of other leukotriene receptor antagonists (eg, zafirlukast, zileuton, pranlukast) in allergic rhinitis and other upper respiratory disorders (ie, nonallergic/vasomotor rhinitis, rhinosinusitis, nasal polyposis, and the common cold) have not been adequately evaluated to date. The overall safety profile of leukotriene receptor antagonists is good.

Decongestants

Decongestants improve nasal ventilation and drainage through an α -adrenergic agonist vasoconstrictor mechanism. Topical decongestants include phenylephrine, pseudoephedrine, oxymetazoline, and xylometazoline. Common topical decongestant side effects include local irritation and rhinitis medicamentosa (drug-induced rhinitis) with extended use.⁸² As a result, expert guidelines recommend that intranasal decongestant treatment be limited to brief use of less than 10 days^{10,83} with switch to other therapies if symptoms persist after 5 days.⁸⁴

Oral decongestants include phenylephrine and pseudoephedrine, with the latter being more effective. In some patients, their use can be associated with adverse systemic effects, including increased blood pressure, palpitations, appetite loss, and insomnia.¹³

Congestion efficacy in allergic rhinitis

Both oral and topical decongestants have proven effective for treating nasal congestion associated with allergic rhinitis. Topical decongestants are the most effective treatment for nasal congestion in subjects with allergic rhinitis, but their adverse effect profile make them suitable for short-term use only.^{6,10,11} Selner and colleagues used fiber-optic rhinoscopy

to measure nasal patency in patients with nasal congestion due to allergic rhinitis. They reported significant symptomatic relief with both oral pseudoephedrine and topical oxymetazoline, which correlated with the total nasal airway area.⁸⁵

A crossover study of asymptomatic patients with perennial allergic rhinitis due to house dust mite exposure compared the efficacy of the topical decongestant xylometazoline with the antihistamine/oral decongestant combination of cetirizine and pseudoephedrine. Following exposure to allergen and 4 days of treatment, the 2 treatments appeared equally effective in alleviating nasal congestion.⁸⁶ Although the topical decongestant had a more rapid onset of action, its effect was short-lived compared with the extended action of the oral drug combination.⁸⁶ The response over 15 minutes to topical oxymetazoline was compared with the response over 28 days to the intranasal corticosteroid mometasone furoate in another crossover study in patients with perennial allergic rhinitis. The magnitude of the response was significantly greater with oxymetazoline than mometasone furoate for both subjective and objective outcomes of nasal obstruction, although there was high variability of response to oxymetazoline.⁸⁷

A randomized, double-blind, 2-week study in patients with seasonal allergic rhinitis due to ragweed demonstrated that the oral decongestant pseudoephedrine was significantly more effective for relief of nasal congestion than the leukotriene receptor antagonist montelukast.⁸⁸ Importantly, the decongestant effect of oral pseudoephedrine in patients with seasonal allergic rhinitis is enhanced when administered in combination with newer H₁-antihistamines, including cetirizine,⁸⁹ desloratadine,^{25,90} loratadine,²⁴ and fexofenadine,²⁶ although the improvements in congestion favoring the combination therapy over oral decongestant alone are not consistently significant. Effective congestion relief with oral pseudoephedrine, alone or in combination with an antihistamine, has also been demonstrated in patients with perennial allergic rhinitis (Figure 2).²³

Congestion efficacy in nonallergic/vasomotor rhinitis

No studies have been published that evaluated the effects of either oral or topical decongestants versus placebo in patients with nonallergic/vasomotor rhinitis.

Congestion efficacy in rhinosinusitis and/or nasal polyposis

While decongestants may provide relief from congestion in rhinosinusitis and/or nasal polyposis, no adequately designed studies have evaluated their efficacy in these conditions.⁷

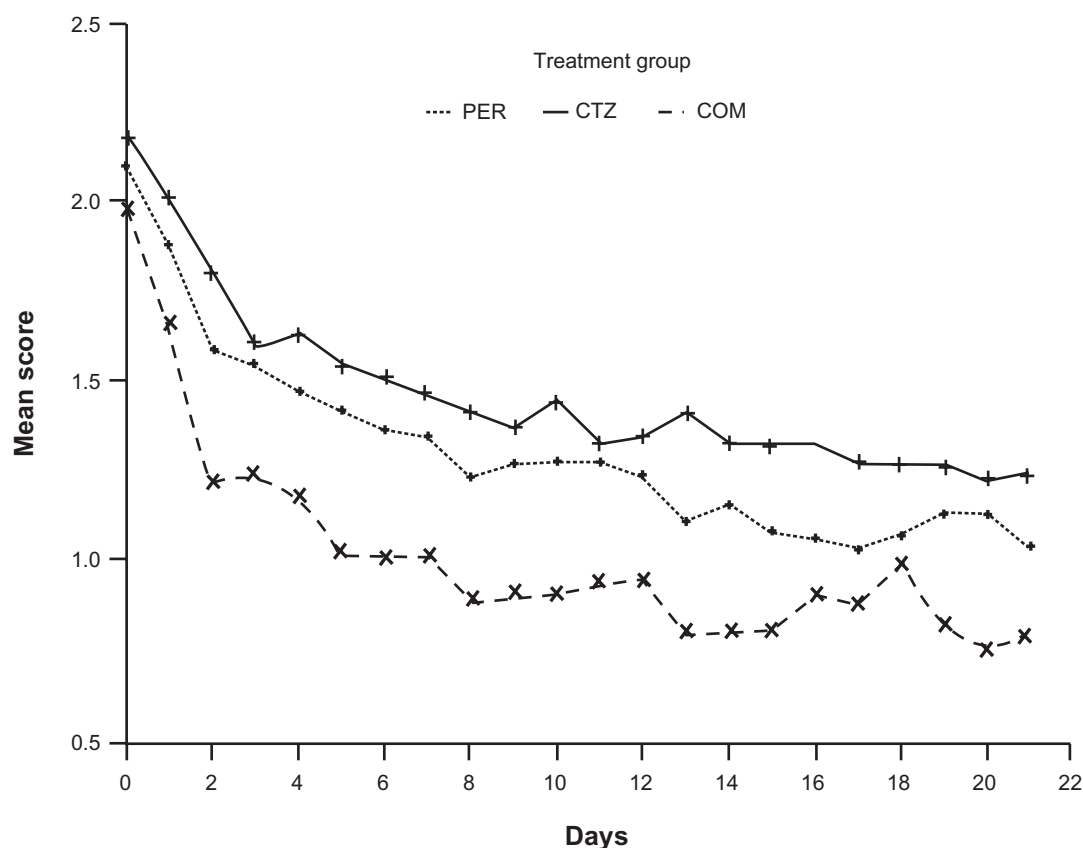


Figure 2 Nasal obstruction mean score versus treatment days. $P < 0.001$ for COM vs CTZ; $P = 0.004$ for COM vs PER; $P = 0.128$ for CTZ vs PER. Reproduced with permission from Bertrand B, Jamart J, Marchal JL, Arendt C. Cetirizine and pseudoephedrine retard alone and in combination in the treatment of perennial allergic rhinitis: a double-blind multicentre study. *Rhinology*. 1996;34(2):91–96.²³ Copyright © 1996 International Rhinologic Society.

Abbreviations: COM, combination of cetirizine and pseudoephedrine; CTZ, cetirizine; PER, pseudoephedrine.

Only a few small studies of decongestants in rhinosinusitis have reported results, and they have failed to demonstrate consistent improvement in congestion. A study comparing topical xylometazoline and oral pseudoephedrine in 10 patients with chronic sinusitis found that the topical agent was more effective for nasal mucosa decongestion, although neither therapy had a significant effect on sinus congestion.⁹¹ A study of 68 children with acute sinusitis treated with amoxicillin for 14 days found that symptoms improved as quickly in patients receiving a placebo as in those receiving an oral decongestant/antihistamine combination.⁹²

Congestion efficacy in the common cold

A Cochrane database meta-analysis assessed the efficacy of topical decongestants in reducing nasal congestion in adults suffering from the common cold, demonstrating a modest but statistically significant 6% decrease in patient-reported symptoms after a single dose of intranasal decongestant compared with placebo.⁹³ In addition, this meta-analysis also reported a statistically significant, 24% reduction in nasal airway

resistance with the use of a decongestant.⁹³ A small increase in the risk of insomnia with pseudoephedrine compared with placebo was one of the few adverse events.⁹³ A double-blind, randomized, placebo-controlled trial in patients suffering from nasal congestion associated with the common cold reported that pseudoephedrine hydrochloride 60 mg 4 times daily for 3 days significantly reduced patient-reported congestion compared with placebo on day 1, but not on day 3.⁹⁴ However, the mean decrease from baseline in congestion/stuffiness over the study duration was significantly greater with pseudoephedrine than with placebo.⁹⁴ A separate single-dose trial reported that oxymetazoline reduced nasal airway resistance and symptoms of nasal blockage within 1 hour in adults with the common cold, and the effect persisted for up to 7 hours.⁹⁵

Safety

The most common side effect of topical decongestants is rhinitis medicamentosa, and it limits the practical utility of these agents to short-term therapy. The most widely used

oral decongestant, pseudoephedrine, is associated with an increased risk of insomnia, and the US Department of Justice has included pseudoephedrine in the Controlled Substances Act, limiting patients' access.⁹⁶

Despite their proven efficacy against nasal congestion associated with allergic rhinitis, the adverse event profile of topical and oral decongestants limits their usefulness in this disease. In addition, the evidence supporting the utility of decongestants for relief of congestion associated with nonallergic/vasomotor rhinitis, rhinosinusitis, or nasal polyposis is very limited. However, these agents may be a more appropriate option for congestion relief related to the common cold, because of the shorter duration of treatment required.

Intranasal corticosteroids

Intranasal corticosteroids have potent and broad anti-inflammatory activities and have demonstrated congestion relief across the spectrum of upper respiratory disorders, including seasonal and perennial allergic rhinitis, nasal polyposis, and both acute and chronic rhinosinusitis.^{6,7,10,11} Available intranasal corticosteroids include beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. Important features of an intranasal steroid include topical potency with low systemic bioavailability, good acute and long-term efficacy, rapid onset of action, low risk of adverse events, and convenient dosing to promote adherence.

Congestion efficacy in allergic rhinitis

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, corticosteroids are currently the most effective anti-inflammatory medication available for the treatment of rhinitis.⁶ In comparative studies, intranasal corticosteroids have shown superior efficacy compared with other medications used to treat nasal congestion. A meta-analysis of 14 controlled trials in patients with allergic rhinitis showed that intranasal steroids provide superior relief of nasal congestion/blockage compared with oral antihistamines (Figure 3A).²⁷ Intranasal steroids also demonstrated greater effectiveness than intranasal H₁-antihistamines in improving nasal blockage in a meta-analysis of 4 studies in patients with allergic rhinitis (Figure 3B).²⁸ A separate meta-analysis of 4 randomized controlled studies comparing leukotriene receptor antagonists and intranasal steroids in patients with allergic rhinitis showed that steroids were more effective for improving composite nasal symptom scores (individual symptom scores, such as congestion, were not reported).⁹⁷ In addition,

several trials have demonstrated superior congestion relief with the intranasal steroid fluticasone propionate versus montelukast in patients with seasonal allergic rhinitis.^{8,73,74}

Numerous studies have demonstrated that intranasal steroids effectively relieve congestion due to seasonal allergic rhinitis. A study of 406 adults and children with seasonal allergic rhinitis found that once-daily intranasal budesonide treatment for 4 weeks significantly reduced nasal congestion.⁹⁸ Similarly, once-daily fluticasone propionate administered to adult patients with seasonal allergic rhinitis for 2 weeks also reduced clinician- and patient-rated scores for nasal obstruction.⁹⁹ In a recent pooled analysis of 4 randomized, double-blind, placebo-controlled studies comprising 982 adult and adolescent patients with seasonal allergic rhinitis, treatment with the intranasal steroid mometasone furoate was significantly more effective than placebo in reducing nasal congestion scores (Figure 4).¹⁰⁰ Mometasone furoate was effective in relieving congestion across all severities of seasonal allergic rhinitis, with the magnitude of the benefit greatest in patients with the most severe congestion (Figure 4).¹⁰⁰ A 2-week study of adults with seasonal allergic rhinitis reported that once-daily treatment with triamcinolone acetonide significantly reduced nasal symptoms, including congestion,¹⁰¹ and a 2-week study including adults and adolescents with seasonal allergic rhinitis reported that once-daily treatment with fluticasone furoate significantly reduced nasal symptoms, including congestion.¹⁰² In a 2-week study of adults and adolescents with seasonal allergic rhinitis, once-daily treatment with ciclesonide significantly reduced total nasal symptoms. However, the individual symptom scores were not reported.¹⁰³

The congestion efficacy of intranasal steroids has been demonstrated across age groups. A study of 249 children with seasonal allergic rhinitis found that fluticasone propionate administered once daily for 4 weeks significantly improved nasal symptoms, including nasal obstruction upon awakening.¹⁰⁴ In another trial conducted in 679 children with seasonal allergic rhinitis, once-daily mometasone furoate also significantly improved nasal congestion.¹⁰⁵

In patients with predictable seasonal allergies, intranasal corticosteroids can be used as prophylactic therapy. Graft et al reported that an 8-week course of mometasone furoate 200 µg once daily initiated before the start of ragweed season significantly delayed the onset of nasal symptoms, including stuffiness/congestion in patients with seasonal allergic rhinitis.¹⁰⁶

Intranasal steroids are also effective for treating nasal symptoms of perennial allergic rhinitis. A study of 550 adult and adolescent patients with moderate-to-severe perennial

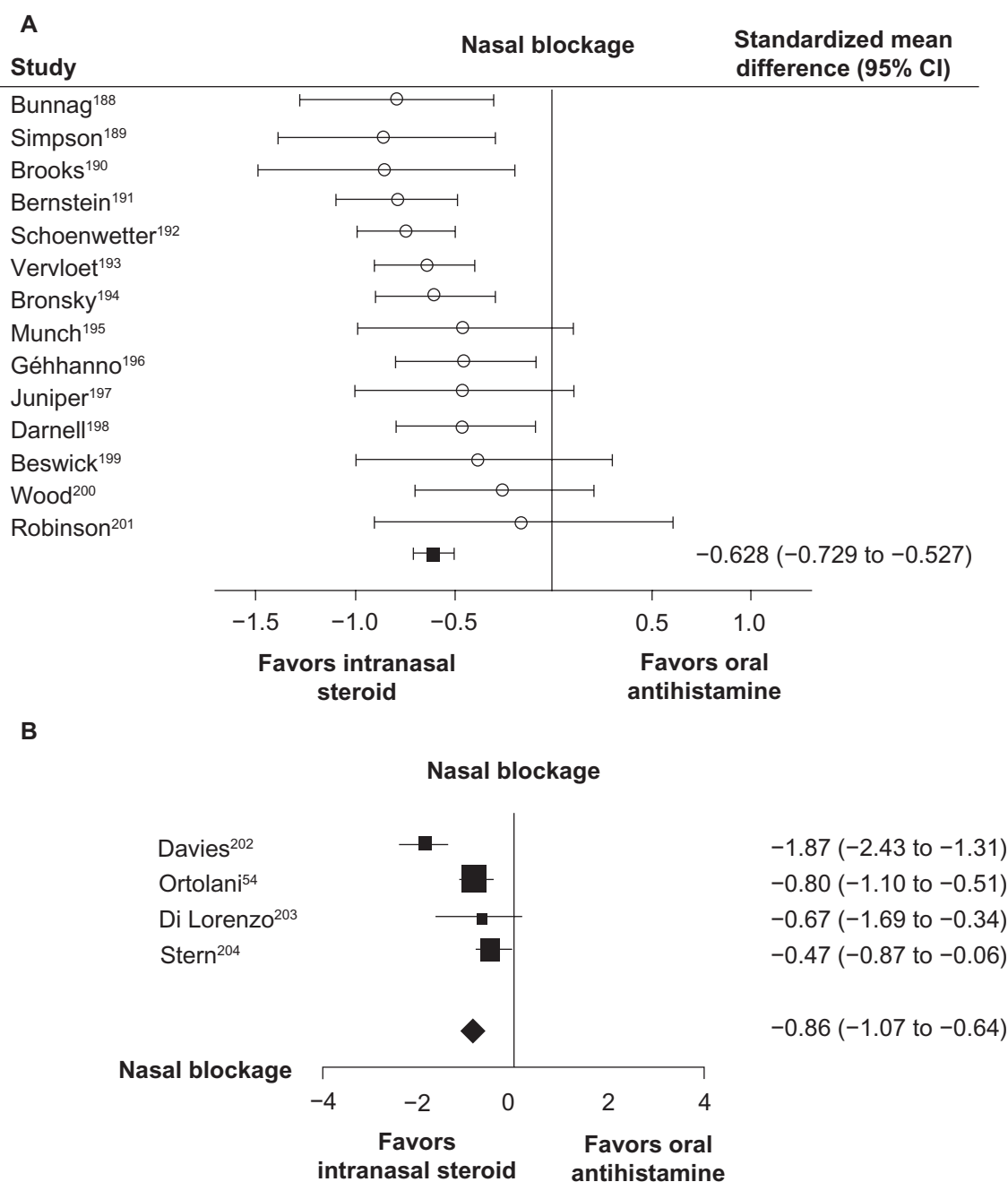


Figure 3 A) Meta-analysis of intranasal corticosteroids versus oral H_1 -receptor antagonists for the treatment of nasal blockage in allergic rhinitis. Intranasal steroids included beclomethasone dipropionate, fluticasone propionate, triamcinolone acetonide, and budesonide. Oral antihistamines included dexchlorpheniramine, terfenadine, astemizole, loratadine, and cetirizine. Adapted with permission from British Medical Journal, Weiner JM, Abramson MJ, Puy RM, volume 317, 1624–1629, Copyright © 1998 with permission from BMJ Publishing Group Ltd.²⁷ **B)** Meta-analysis of intranasal corticosteroids versus topical H_1 -receptor antagonists for the treatment of nasal blockage in allergic rhinitis. Intranasal steroids included beclomethasone dipropionate, fluticasone propionate, and budesonide. Topical antihistamines included azelastine and levocabastine. Adapted with permission from Yáñez A, Rodrigo GJ. Intranasal corticosteroids versus topical H_1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol.* 2002;89(5):479–484.²⁸ Copyright © 2002 American College of Allergy, Asthma and Immunology.

allergic rhinitis found that once-daily treatment with either fluticasone propionate 200 µg or mometasone furoate 200 µg resulted in a significant reduction in patient-rated nasal congestion compared with placebo.¹⁰⁷ A 52-week study of once-daily treatment with ciclesonide in patients with perennial allergic rhinitis demonstrated significant relief of nasal congestion,¹⁰⁸

but no significant congestion benefit of ciclesonide versus placebo was observed in a 6-week study.¹⁰⁹

Pediatric patients with perennial allergic rhinitis have also been effectively treated with intranasal steroids. Recently, fluticasone furoate 55 µg or 110 µg once daily has been reported to reduce total nasal symptom scores in pediatric

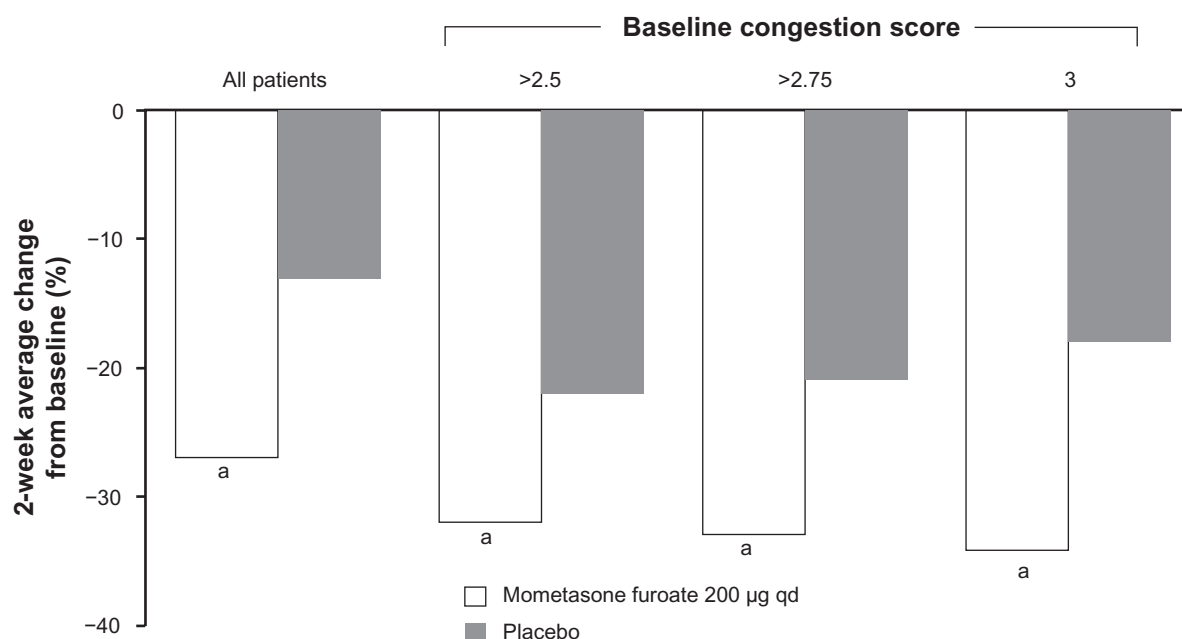


Figure 4 Percent change in congestion symptom score in a pooled analysis of 4 studies with mometasone furoate in seasonal allergic rhinitis. The magnitude of change was greatest in patients with the highest baseline congestion scores. Mean baseline congestion scores in the overall population were 2.24 in the mometasone furoate group and 2.25 in the placebo group. In the >2.5 baseline congestion score group, the baseline scores were 2.83 (mometasone furoate) and 2.84 (placebo). In the >2.75 group, the baseline scores were 2.94 in both the mometasone furoate and placebo groups. * $P < 0.001$ vs placebo. Adapted with permission from Berger WE, Nayak AS, Staudinger HW. Mometasone furoate improves congestion in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Pharmacother*. 2005;39(12):1984–1989.¹⁰⁰ Copyright © 2005 Harvey Whitney Books Co.

patients aged 2 to 11 years with perennial allergic rhinitis, although individual symptom scores were not reported.¹¹⁰ In a previous study of 381 children aged 3 to 11 years with perennial allergic rhinitis, mometasone furoate 100 µg once daily was also significantly more effective than placebo in reducing patient-rated congestion.¹¹¹

Congestion efficacy in nonallergic/vasomotor rhinitis

Intranasal corticosteroids have also been evaluated in the treatment of congestion associated with nonallergic rhinitis. Webb et al assessed the efficacy of fluticasone propionate treatment in 983 patients with perennial nonallergic rhinitis, with or without eosinophilia. They found that fluticasone propionate administered for 28 days was significantly better than placebo in improving total nasal symptoms (nasal obstruction, postnasal drip, and rhinorrhea; individual symptom scores were not reported).¹¹² A 28-day study including 188 patients with nonallergic rhinitis reported that patient-rated nasal congestion scores were significantly reduced during days 22 to 28 of treatment with fluticasone propionate.¹¹³

Congestion efficacy in rhinosinusitis

The anti-inflammatory effect of intranasal steroids has prompted study of these agents in acute and chronic

rhinosinusitis. In light of these studies, European guidelines were published as the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) recommending the use of intranasal steroids for acute rhinosinusitis as monotherapy or as adjunctive therapy to systemic antibiotics with a high level of evidence (I), while noting that there is no evidence for intranasal steroids in the prophylaxis of recurrent acute rhinosinusitis.⁷ EPOS guidelines also note that there is some evidence for intranasal steroid efficacy in chronic rhinosinusitis without polyps, and that intranasal steroids have a high level of evidence (Ia) against nasal symptoms in chronic rhinosinusitis with polyps.⁷

Several studies have demonstrated the efficacy of intranasal steroids as an adjunct to antibiotics in patients with acute rhinosinusitis.^{7,114–118} In 2 studies, patients with acute sinusitis were treated with amoxicillin clavulanate potassium (ACP) for 21 days and randomized to concurrently receive either adjunctive mometasone furoate or placebo.^{114,116} Adjunctive intranasal mometasone furoate therapy was associated with significant improvements in congestion and total symptom scores compared with antibiotic treatment alone.^{114,116} Similar results were found with flunisolide as an adjunct to ACP in patients with acute sinusitis.¹¹⁵ The addition of intranasal flunisolide to oral ACP therapy significantly improved congestion/obstruction scores over 3 weeks in these

patients compared with antibiotic therapy alone (Figure 5).¹¹⁵ Furthermore, nasal cytology revealed that neutrophils, eosinophils, and basophils were all significantly decreased in the flunisolide-treated group.¹¹⁵ Another study evaluated the combination of fluticasone propionate, cefuroxime, and a topical decongestant in patients with acute sinusitis. In this study, the addition of fluticasone propionate produced significantly higher rates of clinical success (defined as “cured” or “much improved”) than the combination of antibiotic/decongestant alone.¹¹⁷ The time to clinical success was also significantly shorter with the addition of fluticasone propionate.¹¹⁷

Corticosteroid/antibiotic combination therapy has also proved effective in pediatric patients. In 151 children with acute sinusitis, nasal discharge and cough were significantly improved in subjects randomized to treatment with budesonide and amoxicillin compared with amoxicillin alone.¹¹⁸ Similarly, significantly higher recovery rates were reported in 52 children with acute maxillary sinusitis who were treated for 10 days with a combination of budesonide plus cefaclor compared with antibiotic therapy plus an oral decongestant.¹¹⁹

In addition to being effective when administered as an adjunct to antibiotics, intranasal steroids are also an effective therapy for congestion in acute rhinosinusitis when administered as monotherapy.¹²⁰ In a study reported by Meltzer et al 981 adults and adolescents with acute rhinosinusitis and symptoms persisting beyond 7 days, but without

symptoms of severe disease, experienced significantly greater improvements in nasal congestion score during days 2 to 15 of the treatment period with mometasone furoate monotherapy than with amoxicillin alone or with placebo.¹²⁰ A study by Lund and colleagues in patients with chronic rhinosinusitis demonstrated significantly greater improvement in congestion with budesonide than with placebo.¹²¹

Congestion efficacy in nasal polyposis

EPOS 2007 guidelines recommend intranasal steroids for the treatment of nasal polyps with a level of evidence of Ia due to their well-documented efficacy in reducing polyp size and relieving symptoms associated with nasal polyposis, including nasal blockage. In 2 small-scale studies, fluticasone propionate nasal spray 200 µg twice daily or beclomethasone dipropionate nasal spray 200 µg twice daily significantly increased nasal inspiratory flow in patients with nasal polyposis.^{122,123} Two large, randomized, placebo-controlled studies demonstrated that mometasone furoate nasal spray 200 µg once daily and particularly 200 µg twice daily significantly improved nasal congestion score at 1 month compared with baseline values, and this improvement persisted throughout the 4-month treatment period.^{124,125} In another study, intranasal fluticasone propionate nasal drops 400 µg once daily were also significantly more effective than placebo for reducing nasal blockage after 3 months of treatment in patients with bilateral nasal polyposis.¹²⁶ Topical corticosteroids are recommended

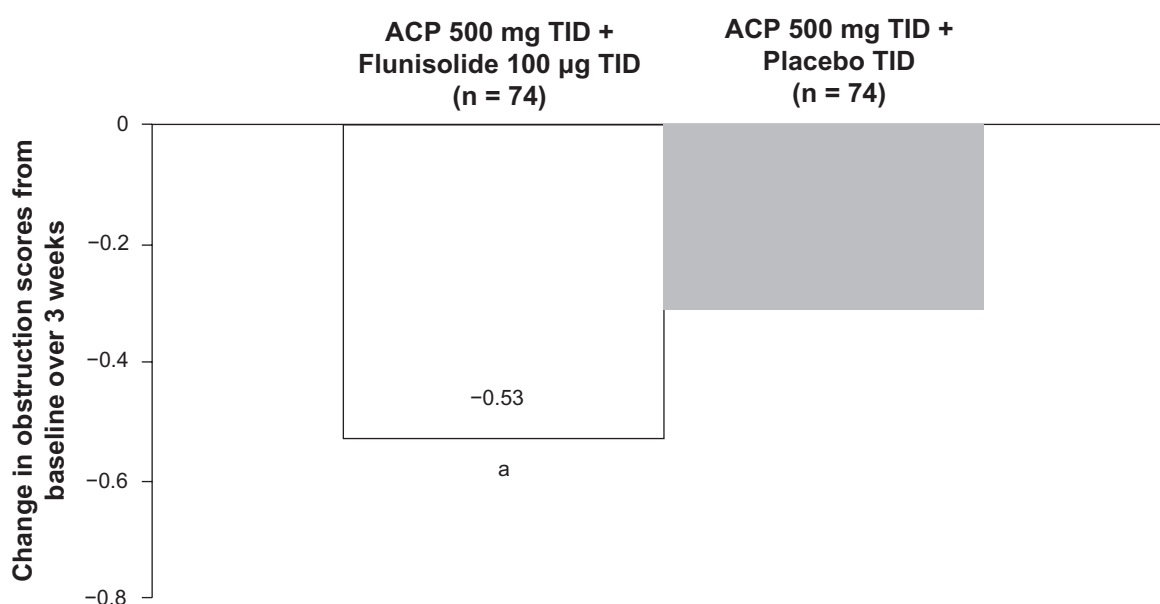


Figure 5 Mean change in turbinate swelling/obstruction score over 3 weeks in patients with acute rhinosinusitis treated with amoxicillin clavulanate potassium (ACP) 500 mg 3 times daily (TID) and either flunisolide 100 µg 3 times daily or placebo 3 times daily. * $P = 0.041$ versus ACP 500 mg 3 times daily + placebo TID. Reprinted from *J Allergy Clin Immunol*, Vol 92, Meltzer EO, Orgel HA, Backhaus JW, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. Pages 812–823, Copyright © 1993, with permission from Mosby-Year Book, Inc.¹¹⁵

in the long-term for all patients with inflammatory polyps unless there is a compelling contraindication.¹²⁷

Congestion efficacy in the common cold

The evidence for the efficacy of intranasal steroids against congestion associated with the common cold is limited, as only 2 such studies were reported in the literature. One double-blind, randomized, placebo-controlled study in young adults with the common cold reported that high-dose fluticasone propionate 200 mg 4 times daily for 6 days significantly reduced nasal congestion on some but not all study days.¹²⁸ Another trial found that intranasal beclomethasone dipropionate 400 µg/day failed to reduce symptoms caused by inflammation, such as congestion.¹²⁹

Safety

Although the efficacy of intranasal corticosteroids is well established, these agents are frequently underused due to concerns about potential systemic adverse effects that are thought to be related to their systemic bioavailability. The systemic bioavailabilities of fluticasone propionate, fluticasone furoate, and mometasone furoate are low to undetectable (<1%, 0.5%, and ≤0.1%, respectively) indicating a low potential for systemic side effects, especially compared with oral steroids and older intranasal agents within the drug class.^{130–132} The systemic bioavailability of other intranasal steroids ranges from roughly 10% for budesonide¹³³ to 44% for beclomethasone dipropionate.¹³⁴ Triamcinolone acetonide has a mean peak plasma concentration of approximately 0.5 ng/mL at 1.5 hours postintranasal administration of a single 220 µg dose,¹³⁵ and the absolute bioavailability of the inhaled formulation is 25%, which is predominantly due to the swallowed portion.¹³⁶

Differences in the systemic bioavailability of intranasal steroids stem from a number of factors. Low circulating levels of some steroids might be due to minimal absorption across the nasal mucosa of these agents. Bioavailability may also vary with the proportion of drug absorbed by the gastrointestinal tract. However, a significant portion of each intranasal steroid dose is swallowed, so that differences in the extent of first-pass hepatic inactivation seem to account for most of the diversity in systemic bioavailability across agents.¹³⁷

Clinically significant inhibition of the hypothalamic-pituitary-adrenal (HPA) axis is a potentially serious consequence of systemic exposure to corticosteroids. Using cortisol concentrations as an indicator of HPA activity, mometasone furoate was found to have no effect on cortisol secretion in adults, even when the drug was administered at 20 times the

recommended dose.¹³⁸ Additionally, a study of children aged 3 to 12 years who were treated with intranasal mometasone furoate for up to 14 days found no significant effect on mean plasma cortisol concentrations.¹³⁹ Intranasal triamcinolone acetonide was also found to have no statistically significant effect on urine cortisol/creatinine ratios in a study of 59 children with a mean age of 7.2 years.¹⁴⁰ Although this same study reported small but detectable differences in plasma cortisol levels with fluticasone propionate,¹⁴⁰ additional studies have demonstrated no detectable effects on the HPA axis following short-term intranasal triamcinolone acetonide or fluticasone propionate at their recommended dosages.¹⁴¹ Several studies with fluticasone furoate have reported small, variable changes in cortisol levels compared with placebo, which taken in whole cannot eliminate a potential effect of fluticasone furoate on adrenal function, especially in pediatric patients.¹³² To minimize the potential risk of systemic side effects of any intranasal steroid, each patient's dose should be titrated to the lowest dose that effectively controls symptoms.

Systemic corticosteroid exposure can cause a reduction in growth velocity in pediatric patients, even in the absence of detectable effects on HPA-axis function.¹⁴² A study of 100 prepubescent children aged 6 to 9 years found that 1 year of intranasal beclomethasone dipropionate treatment resulted in detectable growth suppression.¹⁴² The mean change in standing height at study end point was 5.0 cm and 5.9 cm in beclomethasone- and placebo-treated children, respectively.¹⁴² However, a 1-year growth study of 108 prepubescent children aged 3 to 9 years reported no statistically significant difference in growth velocity in patients receiving intranasal fluticasone propionate compared with placebo, and no evidence of clinically relevant changes in HPA-axis function or bone mineral density.¹³⁰ Additionally, neither intranasal triamcinolone acetonide nor fluticasone propionate were found to have significant effects on short-term lower-leg growth velocity in a 2-week study.¹⁴⁰ A long-term study noted no suppressive effect on growth over 1 year in 98 children aged 3 to 9 years treated with mometasone furoate.¹⁴³

There are concerns that long-term corticosteroid use might result in atrophic changes in the nasal mucosa. However, no evidence of adverse changes in the nasal mucosa, including atrophy or epithelial thickness, were noted after 12 months of daily treatment with mometasone furoate 200 µg.¹⁴⁴ Similarly, treatment with intranasal triamcinolone acetonide 220 µg daily for 6 months did not cause atrophy of the nasal mucosa or impairment of mucociliary function in patients with perennial allergic rhinitis.¹⁴⁵

Despite the fact that intranasal steroids are the most effective therapy for symptoms associated with allergic rhinitis, they tend to be underused, especially in pediatric patients, due to concerns over potential side effects. However, the low to negligible systemic bioavailabilities of newer intranasal steroids, in conjunction with the abundance of clinical trial evidence, suggest that these concerns may be somewhat exaggerated. Based on clinical trials that enrolled adult, adolescent, and pediatric patients with allergic rhinitis, the incidence of adverse events associated with the use of currently marketed intranasal corticosteroids was generally low and similar to placebo.^{130–135} Numerous studies have demonstrated that intranasal corticosteroids offer effective relief of nasal congestion in seasonal allergic rhinitis and perennial allergic rhinitis, and can even be used to prevent nasal congestion associated with seasonal allergic rhinitis when given before the start of allergen season. Intranasal corticosteroids have also provided relief of congestion associated with nonallergic rhinitis and have demonstrated superior efficacy with respect to congestion relief in patients with acute rhinosinusitis, both when used as an adjunct to antibiotics and as monotherapy. In addition, intranasal corticosteroids provide effective congestion relief in patients with nasal polyposis. Further evaluation of their ability to relieve congestion associated with the common cold is needed.

Although intranasal steroids are the most effective agents for the relief of congestion associated with allergic rhinitis, there is room for improvement in this treatment class. Mean nasal congestion scores are not reduced to normal levels in clinical trials with these agents, and congestion is not effectively reduced in all patients. Systemic availability is very low for some intranasal steroids, but for others it can be quite substantial, leading to safety concerns.

Other pharmacotherapies

Cromolyn prevents inflammation through its inhibition of mast cells, macrophages, eosinophils, monocytes, and platelets.¹⁴⁶ While cromolyn is an effective treatment for symptoms of sneezing, rhinorrhea, and nasal itching in patients with allergic rhinitis, it is less efficacious against nasal obstruction.⁶ In addition, its decongestant effect is inferior to that of intranasal steroids, such as mometasone furoate.⁵⁵ Cromolyn has a good safety record and is available without prescription.¹⁴⁷ Intranasal cromolyn sodium has not been proven effective for treatment of congestion associated with other upper respiratory diseases, including nonallergic/vasomotor rhinitis and the common cold, as well as rhinosinusitis and/or nasal polyposis.⁷

A topical form of aspirin, lysine-aspirin, has been used in the treatment of nasal polyposis. Objective assessments showed that lysine-aspirin had significant clinical benefit in improving nasal blockage and reducing polyp size when used in addition to topical corticosteroids,¹⁴⁸ possibly related to a reduction in leukotriene receptors.¹⁶

Because parasympathetic nervous system activation induces watery secretion and vasodilatation, it has been postulated that topical anticholinergics may provide efficacy against nasal congestion. However, randomized, controlled trials have shown that the anticholinergic ipratropium bromide provides no relief of nasal obstruction in patients with perennial allergic and nonallergic/vasomotor rhinitis.^{6,149,150} In addition, the systemic bioavailability of intranasal ipratropium (7% to 18%)¹⁵¹ is much higher than that of the second-generation intranasal corticosteroids, including fluticasone propionate, mometasone furoate and fluticasone furoate, and thus increases the potential for systemic side effects. As patients with perennial rhinitis typically suffer from a variety of symptoms, including nasal congestion, itching, and sneezing, other therapeutic agents are preferable as first-line treatment in the majority of patients with allergic rhinitis.⁶

Oral methylprednisolone has been shown to provide significant relief of nasal congestion in patients with moderate-to-severe seasonal allergic rhinitis symptoms compared with placebo over a 1-week treatment period.¹⁵² In addition, it has demonstrated the ability to relieve a nonvascular component of allergic congestion that is unaffected by decongestant therapy.¹⁵³ However, systemic steroids should not be used as first-line treatment for allergic rhinitis, but only as a therapy of last resort when other therapeutic options have been exhausted.⁶ Oral corticosteroids have also been evaluated in acute rhinosinusitis, but there is little evidence to support their use for purposes other than pain relief.⁸⁴ Although no data is available for their efficacy in chronic rhinosinusitis without nasal polyps, recent studies show that short courses of oral corticosteroids reduce polyps and improve congestion in most patients with chronic rhinosinusitis and polyps.^{7,154} From a safety perspective, for nasal congestion, systemic corticosteroids should be limited to short-term use due to their side-effect profile,⁶ which effectively reduces the clinical usefulness of these agents. In addition, systemic steroids should be limited as much as possible in children, and avoided in pregnant women and in patients with a known contraindication.⁶

The C-fiber stimulant capsaicin has also been tested as a therapeutic option for relief of nasal congestion. It has been suggested that the therapeutic effect of capsaicin could be

mediated by C-fiber desensitization through continuous stimulation. A study in adult patients with severe, chronic nonallergic rhinitis receiving intranasal capsaicin under local anesthesia once weekly for 5 weeks reported a significant improvement in nasal obstruction throughout a 6-month follow-up period.¹⁵⁵ However, in a separate randomized, double-blind, placebo-controlled trial in adults with nonallergic rhinitis, capsaicin provided no relief of nasal congestion.¹⁷

Menthol is an alcohol that has been widely used for the relief of nasal symptoms in various upper respiratory diseases. A double-blind, randomized trial in patients with nasal obstruction due to the common cold found that oral administration of a lozenge containing 11 mg of menthol increased patient's sensation of airflow 10 minutes after lozenge administration, but this effect did not persist.¹⁵⁶ Additionally, menthol did not have an impact on nasal resistance to airflow.¹⁵⁶

There is mounting evidence that nasal irrigation with saline is beneficial in treating nasal symptoms in acute and chronic rhinosinusitis, when used as a sole modality or as adjunctive therapy, although such treatment is less effective than intranasal corticosteroids.^{7,83,157,158} Various mechanisms, including improved mucous clearance, may account for the improvement.¹⁵⁷ Recent controlled trials in both children and adults with rhinosinusitis and allergy show that saline washouts significantly relieved nasal congestion and other symptoms as well as improved sleep and quality of life.^{159,160}

Immunotherapy

Immunotherapy for allergic rhinitis involves periodic exposure, usually weekly by subcutaneous injection (SCIT) or daily by sublingual tablet or drops (SLIT), to incrementally larger doses of allergen(s).^{20,161–163} A maintenance dose is usually continued long-term with SCIT at intervals of 2 to 6 weeks,²⁰ and allergen(s) may be modified with adjuvant agents to enhance allergen immunogenicity.^{20,161} Immunotherapy offers a number of advantages over conventional pharmacotherapy, as it appears to offer some benefit in cases of severe allergic rhinitis,²⁰ and its clinical efficacy can be maintained for years after treatment discontinuation.¹⁶¹ In addition, immunotherapy may reduce the risk of developing asthma in patients with allergic rhinitis¹⁶¹ and may prevent new sensitizations.¹⁶¹ A study by Durham et al evaluated the long-term efficacy of grass pollen SCIT in patients who responded favorably to treatment for up to 4 years. After discontinuation of therapy for 3 years, symptom scores and rescue medication scores remained at low levels and were similar to those of patients who continued immunotherapy.¹⁶⁴

SCIT has been shown to effectively reduce nasal congestion in allergic patients. A double-blind, placebo-controlled trial in patients allergic to *Parietaria* found that treatment with an alum adsorbed partially purified *Parietaria* extract (*Alpare parietaria*) for 2 years significantly decreased nasal blockage in the actively treated immunotherapy group compared with placebo.¹⁶⁵ Similarly, a randomized, double-blind, placebo-controlled study in adults with a history of severe grass pollen allergy not controlled by standard antiallergic drugs found that administration of a depot grass pollen extract (timothy grass, *Phleum pratense*) significantly reduced blocked nose during the pollen season compared with placebo.¹⁶⁶

Similar to SCIT, SLIT has also demonstrated congestion relief in subjects with allergic rhinitis. An older study investigating the utility of oral ragweed immunotherapy reported that nasal symptom scores during the natural allergen season were numerically but not statistically lower in the SLIT group versus the placebo group.¹⁶⁷ However, a more recent double-blind, placebo-controlled study of 634 patients with allergies to timothy grass pollen demonstrated that sublingual timothy grass tablet significantly improved all ocular and nasal symptom scores, including blocked nose.¹⁶⁸ Timothy grass tablet SLIT has also proven effective when initiated prior to the allergy season and continued throughout the pollen season.^{162,169} A recent multinational, randomized, double-blind, placebo-controlled study performed in 628 grass pollen–allergic patients reported that treatment with a SLIT tablet containing a mixture of equal proportions of 5 grass pollens (including orchard grass, meadow grass, perennial ryegrass, sweet vernal, and timothy) initiated 4 months before the pollen season and continued throughout the season significantly reduced nasal congestion scores compared with placebo.¹⁷⁰ In addition to the efficacy of grass tablet SLIT on nasal congestion in patients with seasonal grass allergies, house dust mite SLIT has also been shown to reduce nasal blockage in patients with perennial allergic rhinitis. Patients with perennial rhinitis related to house dust mite sensitization randomized to receive house dust mite SLIT for 2 years reported significant improvements in congestion scores versus placebo after 1 year, and these improvements persisted at the end of the second year.¹⁷¹

Potentially fatal anaphylaxis is the most serious clinical concern surrounding the use of allergen immunotherapy.¹⁶¹ Cases of fatal anaphylactic reactions have been reported with the use of SCIT,²⁰ but not with SLIT tablets. The proportion of patients receiving SCIT who suffer systemic reactions is estimated at 5% to 10%.²⁰ With SLIT tablets, the most common adverse events include swelling and itching of the ears,

mouth, and throat, which are typically mild in severity and resolve spontaneously after a short period of time.^{164,168,169} Because of the potential for fatal or near-fatal anaphylactic reaction to immunotherapy, SCIT is always administered in a physician's office with ready availability of epinephrine for rescue, whereas SLIT tablets have been designated to be given under a physician's supervision on the first 1 or 2 occasions, but can be taken by the patient on their own at home thereafter.

Immunotherapy is specifically designed to treat both seasonal and perennial allergic rhinitis and has demonstrated efficacy against nasal congestion in both conditions. However, concerns related to SCIT, including potential for anaphylaxis, uncertainty concerning the strength of administered extracts, the discomfort and expense of frequent injections with SCIT, and patient inconvenience, have limited its adoption in clinical practice.²⁰ Despite these problems, immunotherapy may be indicated for patients with allergic rhinitis if the relief achieved with pharmacotherapy is inadequate or to reduce disease progression, as immunotherapy is the only intervention that alters the natural history of allergic disease.²⁰ In addition, the recent introduction of fixed-dose tablet SLIT may offer an effective and potentially safer and more convenient alternative to SCIT.

Surgical treatments

Surgical treatment for nasal congestion should be reserved for severe or persistent cases of nasal obstruction. The relevant anatomical sites for surgical intervention include the nasal septum, nasal valve, inferior and middle turbinates, and nasopharynx. The nasal septum can interfere with nasal airflow when it is skewed from its midline position, either unilaterally or bilaterally. Deformity of the septum can be due to curvatures of anterior cartilages, spurring or displacement of bony nasal supports, or both. Among available surgical procedures for improving nasal obstruction caused by septal deformity are septoplasty and submucous resection of the septum.

The long-term benefits of septal surgery have been described in a number of studies.^{172–174} A trial in patients diagnosed with a septal deviation requiring surgery to eliminate obstruction reported a statistically significant increase in volume as measured by acoustic rhinometry and a decrease in symptomatic congestion.¹⁷² In addition, a 2- to 3-year follow-up study of patients who underwent septoplasty found significant improvement in nasal breathing and congestion.¹⁷³ A retrospective study found a high degree of patient satisfaction in those who had undergone septoplasty for nasal obstruction 3 months earlier.¹⁷⁴

Anatomical regions of the nasal airway that dynamically affect nasal breathing include the external nasal valve and the internal nasal valve. The nasal valve is the narrowest portion of the nasal airway and accounts for 50% of normal nasal resistance. Collapse of the nasal valve with inspiration (alar collapse) is a common cause of nasal obstruction. Surgical repair of this area can improve nasal airflow and decrease obstruction/ congestion.¹⁷⁵

The nasal turbinates are paired bilateral structures arising from the ethmoid and maxillary bones. Turbinate hypertrophy can include bony structures with or without mucosal swelling, which can be differentiated by acoustic rhinometry pre- and postnasal decongestion. Surgery should be reserved for correcting bony structural problems or mucosal swelling that has failed to remit with maximal medical therapy, including use of oral corticosteroids. Various procedures have been used to reduce turbinate bulk, including turbinectomy (resection and surgical reduction of the turbinates), submucous resection of turbinate bone, submucosal diathermy, laser ablation, and radiofrequency ablation.^{176,177}

A number of positive outcomes have been reported in patients who have undergone turbinate surgery. The procedure has been reported to improve nasal airflow,^{177,178} reduce symptoms of nasal obstruction,^{177,179,180} and increase nasal cavity volume.¹⁸⁰ Although turbinate surgery is effective in properly selected patients, the procedure is subject to a number of drawbacks, including persistent nasal problems as the result of less aggressive procedures. On the other hand, complications of overly aggressive or complete turbinectomies include the risk of atrophic rhinitis and “open nose.”¹⁸¹ In addition, postoperative development of dry rhinitis characterized by the accumulation of stagnant secretions resulting from excessive removal of the inferior turbinate has also been reported.¹⁸¹

Adenoid hypertrophy can affect nasal airflow by causing posterior nasal/nasopharyngeal obstruction. In many patients, especially children, adenoid hypertrophy is associated with hypertrophy of the inferior turbinates,¹⁸² suggesting that adenoidectomy might improve symptoms of nasal obstruction in these patients. While adenoidectomy has been shown to decrease nasal congestion and improve nasal airflow in children,^{182,183} its role in adults is limited.

A major symptom of chronic rhinosinusitis is nasal congestion, and endoscopic sinus surgery (ESS) has been performed in such cases as a means of relieving congestion. The benefits of ESS in patients with chronic rhinosinusitis have been demonstrated in a number of studies. ESS produced significant improvements in symptoms including congestion and nasal obstruction,^{184,185} and in quality-of-life measures.¹⁸⁶

Patients who underwent ESS for chronic sinusitis also had significantly improved nasal endoscopy scores.¹⁸⁶ Based on comparisons of pre- and postoperative rhinometry and rhinomanometry, ESS produces an increase in nasal cavity volumes and a decrease in nasal inspiratory resistance.^{185,187}

Surgery remains an important treatment option for congestion, particularly in subjects with inadequate response to prior therapeutic modalities or those with structural abnormalities. The potential benefits of surgical approaches should be weighed against the risk for complications.

Treatment of less common specific rhinopathies

In addition to the common rhinopathies of allergic rhinitis and acute and chronic sinusitis, there are a number of specific nasal conditions that are associated with symptoms of nasal congestion. Several of these are listed in the Table 1, along with recommendations for their treatment.

Summary

Congestion is a cardinal symptom of upper respiratory diseases and is often a focus of treatment. In all cases, a stepwise approach is recommended for the management and treatment of congestion, consisting of (1) diagnosis of the cause(s), (2) patient education and monitoring, (3) avoidance of environmental trigger factors where possible, (4) pharmacotherapy, and (5) allergen immunotherapy (only in patients with allergic rhinitis) or surgery for patients in whom the condition cannot be controlled with the previous measures.

A variety of pharmacologic therapies are available for the treatment of nasal congestion in various upper respiratory diseases, such as allergic rhinitis, nonallergic/vasomotor rhinitis, rhinosinusitis, nasal polyposis, and the common cold. The most extensively evaluated therapies for congestion

include antihistamines, decongestants, leukotriene receptor antagonists, and intranasal corticosteroids. Intranasal steroids are currently the most effective medication available for the treatment of congestion associated with allergic rhinitis and have also demonstrated effective congestion relief in other upper respiratory diseases. It is important to note that while intranasal steroids have proven to be more effective than other classes of agents for the relief of congestion in controlled clinical trials, they do not reduce mean nasal congestion scores to normal levels, nor do they effectively reduce congestion in every patient. Thus, the efficacy of a particular therapeutic selection should be evaluated for each patient, with clinical trial results and comparison studies informing therapy considerations and helping to establish expectations.

Immunotherapy has emerged as an effective option for those patients with allergic rhinitis in whom pharmacotherapy is insufficient, while surgery may be warranted in cases of severe refractory congestion or in patients with structural abnormalities. Treatment of less common rhinopathies should be tailored to the individual diagnosis and the needs of the particular patient.

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Table 1 Treatment of some less common rhinopathies

Condition	Recommendation
Occupational rhinitis	Identify and avoid the irritant or allergen
Nasal polyps	Assess for underlying infection, aspirin sensitivity, fungal or bacterial hypersensitivity, cystic fibrosis, vasculitis, or other complicating disease Consider therapy with intranasal corticosteroids, antileukotrienes, antibiotics, topical aspirin, surgery
Rhinitis medicamentosa	Treat with intranasal or oral corticosteroids. Wean off intranasal decongestants
Aspirin-exacerbated respiratory disease (aspirin intolerance), including aspirin-induced rhinosinusitis and/or asthma	Avoid aspirin and other nonsteroidal anti-inflammatory drugs. Consider topical aspirin or oral aspirin desensitization
Nasal congestion during pregnancy	Consider Breathe Right® nasal strips at night instead of medications
Nasal septal deviation	If obstruction is severe and persistent, consider surgical consultation

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