

Advances in allergy management

Our understanding of the pathophysiology of allergy has moved to the molecular level, while study of epidemiology and genetics has revealed risks of developing allergies based on environmental and genetic profiles, and pharmacoeconomic data have enabled accurate measurement of the immense burden of allergic disease. These advances in allergy research have affected its management, particularly the search for new antiallergy therapies. New therapies should intervene in the systemic allergy inflammatory cascade and provide clinical efficacy that extends to multiple allergic disease states. In addition, these new therapies should present no additional safety issues, offer improvements over existing therapies, and have an impact on disease-impaired quality of life. *In vitro* studies show that desloratadine, a new, once-daily, nonsedating, selective histamine H₁-receptor antagonist, blocks the systemic allergy cascade at multiple points. Desloratadine 5 mg once daily relieves the symptoms of chronic idiopathic urticaria and of both seasonal (SAR) and perennial allergic rhinitis. In patients with concomitant asthma and SAR, asthma symptoms are relieved and β_2 -agonist medication use is decreased by desloratadine. Unlike many other second-generation histamine H₁-receptor antagonists, desloratadine provides the added benefit of efficacy against nasal obstruction in SAR. Desloratadine improves quality of life by decreasing the impact of allergic symptoms on sleep and on daily activities.

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Since the early 1990s, several advances have been made in the biomedical research and medical treatment of allergy. Understanding of the pathophysiology of allergy has moved to the molecular level, enabling the discovery of new treatment targets and new tools to assess drug efficacy and safety. The fields of epidemiology and genetics have converged to reveal risks of developing disease, based on environmental and genetic profiles. This may allow the identification of those at risk before the disease is clinically apparent. Pharmacoeconomic studies allow both the costs of illness and the benefits of wellness to be measured, thus enabling accurate measurement of the burden of allergic disease.

In this article, the effect of advances in the biomedical research of allergy is illustrated with data on desloratadine, a new selective histamine H₁-receptor antagonist.

Advances in biomedical research of allergy

Pathophysiology

Allergy is now understood to be a systemic inflammatory disease (Fig. 1). Multiple inflammatory mediators have been identified (1–3). These include cytokines, such as the interleukins (IL-3, IL-4, IL-5, IL-9, and IL-13), which promote the production of

immunoglobulin E (IgE), airway hyperresponsiveness, the overproduction of mucus, and the development of eosinophils and mast cells, all of which are associated with chronic allergic inflammation. Other inflammatory mediators that have been identified are chemokines, such as 1) eotaxins, 2) RANTES (regulated on activation, normal T cell expressed and secreted), 3) monocyte chemo-attractant proteins (e.g. MCP-2 and MCP-3) (3), and 4) thymus- and activation-regulated chemokine (TARC) (4,5). These chemotactic cytokines have the ability to attract and activate leukocytes. Adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), and selectins (e.g. selectin-P, selectin-E) (3,6), are surface ligands that mediate cell-to-cell adhesion and diapedesis. Chemokines recruit eosinophils and basophils, and adhesion molecules promote the accumulation of inflammatory cells, processes that are central to the maintenance of chronic allergic inflammation.

Epidemiology and genetics

The prevalence of allergic rhinitis varies widely, from 1% to 40%, according to the population studied and to the conditions and methods of assessment (3). Prevalence varies widely in different

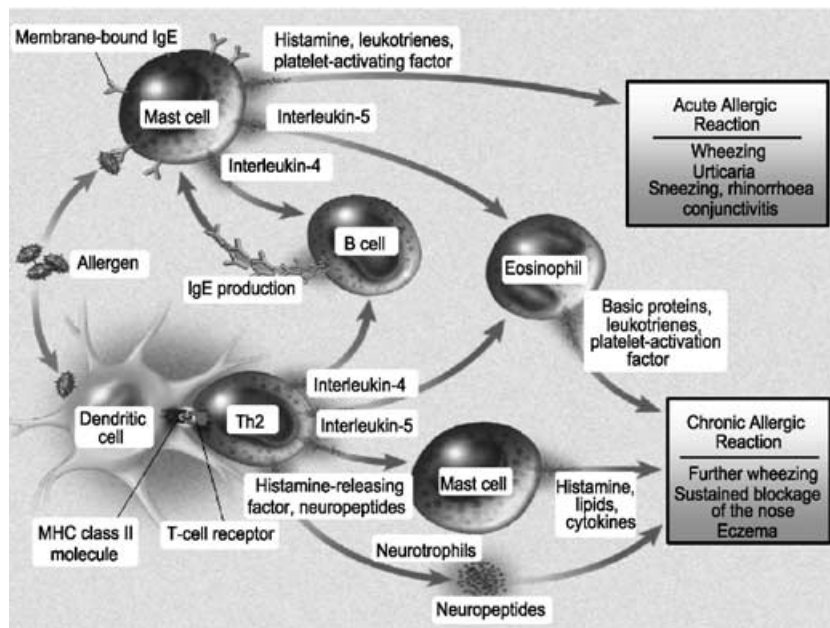


Figure 1 Pathways leading to acute and chronic allergic reactions. Acute allergic reactions are due to the antigen-induced release of histamine and lipid mediators from mast cells. In the skin and upper airways, basophils (not shown) may also participate in allergic tissue reactions. Chronic allergic reactions, including the late-phase reaction, may depend on a combination of pathways, including the recruitment of eosinophils, the liberation of mast cell products by histamine-releasing factors, and neurogenic inflammation involving neurotrophins and neuropeptides. MHC, major histocompatibility complex. Adapted from (1).

geographic locations; worldwide, the 1-year prevalence ranged from 0.8–14.9% among children aged 6–7 years, and from 1.4–39.7% among adolescents aged 13–14 years (7). Furthermore, the incidence and prevalence of allergy has been rising in many countries (8–11).

The systemic nature of allergy is highlighted by the increased risk, among patients who already have an allergic disease, of developing other allergic diseases (12). Further evidence of a comorbid association is provided by the extremely high prevalence of asthma among patients with allergic rhinitis (2). Large longitudinal epidemiological studies have found that allergic rhinitis generally precedes the onset of asthma (13–15), although disease occurs throughout the airways (16); 30–80% of asthmatic patients have allergic rhinitis, and 20–40% of those with allergic rhinitis have asthma (17).

Geographic variation in the prevalence of allergy and the increasing prevalence with time imply environmental influences. It has been suggested that improvements in hygiene and the use of vaccinations and antibiotics to control infections in early life may deprive the developing immune system of exposure to microbial antigens, which is necessary to stimulate Th1 lymphocytes and prevent immune dominance by Th2 lymphocytes. Atopic (IgE-mediated) allergic disease is characterized by immunopathological dominance by Th2 lymphocytes (1). Based on the assumption that older siblings act as vectors for microbial exposure of younger children, the “hygiene” theory is supported by the findings that young children with older siblings are less likely to suffer from atopic allergic diseases or to develop asthma and wheezing (18–20). Th2 lymphocyte dominance may also be favoured

by neonatal allergen sensitization via diet or birth during the pollen season, or even by antenatal allergen sensitization via maternal exposure (21–24).

In addition to environmental factors, multiple genetic factors have been linked to atopic allergic diseases, although the latter may be heterogeneous between different ethnic groups (25,26). Furthermore, triggering cofactors may be necessary for disease manifestation in persons with an underlying genetic predisposition and who are susceptible because of environmental priming. Genetic factors that have been identified include the presence of specific HLA alleles and polymorphisms of the high-affinity receptor for IgE (*FcεRI*), the IL-4 family of cytokine genes, cluster of differentiation 14 (CD14), and other loci (21,27–30). Triggering cofactors may include respiratory viral infection and exposure to allergens, tobacco smoke, and air pollutants (31–34).

Pharmacoeconomics

The economic costs of allergy are enormous. Allergic disease results in not only significant healthcare expenditure (direct costs) but also costs to society because of decreased work efficiency and increased absenteeism (indirect costs). Furthermore, the burden of allergic diseases on people can cause important decreases in psychosocial well-being.

Allergic rhinitis is estimated to cost billions of euros/dollars (€/€) annually in direct and indirect costs (35–38). In addition to increased absenteeism, the quality and quantity of work produced declines because of decreased cognitive function (learning, memory, and decision-making) and psychomotor

function. Over-the-counter allergy medications with sedative effects further compromise cognitive function and, subsequently, productivity (38). The consequences of allergic rhinitis on psychosocial well-being are illustrated by its association with higher rates of depression and anxiety disorder, as revealed by analysis of a healthcare claims database of more than 600 000 privately insured people in the USA (39). In the latter study, prescription treatment of allergic rhinitis moderated the increased healthcare expenditure associated with psychological comorbidity.

The economic effect of asthma is also immense. The annual direct healthcare costs and indirect costs of asthma were estimated to approach €/ \$1 billion in Switzerland in 1997 (40), to approach €/ \$3 billion in Germany in 1996, even without inclusion of the cost of outpatient physician services (41), and to exceed €/ \$10 billion in the USA in 1994 (42). Direct medical costs for asthma exceed indirect medical costs in both Europe and the USA (40,42–44). In European studies published within the last few years, the estimated total direct and indirect costs annually per patient have ranged from approximately €/ \$2000 to €/ \$3000 (45–47). Estimated annual direct and indirect costs per patient increased several-fold with increasing disease severity from mild to severe (46,48). Estimated costs were higher in the elderly than in other adults, reflecting greater severity of disease, and measures of quality of life were significantly worse ($P < 0.001$) (49). Also, estimated costs were higher in adults than in children, likely reflecting losses in productivity (47,48). Employed people with asthma are estimated to lose an average of 12 days of productivity annually (50).

Changing the management of allergy

Ideally, antiallergy therapies should target the systemic allergy cascade, demonstrate broad clinical efficacy in multiple disease manifestations of allergy, show improved clinical efficacy over existing therapies with no additional safety issues, and have an effect on disease-impaired quality-of-life measures.

Targeting the systemic allergy cascade

The systemic nature of allergy demands targeting of the broad systemic allergy cascade. Many new and experimental treatment options have been designed to target specific inflammatory mediators of the allergy cascade, including IgE, cytokines, integrins (for which cell adhesion molecules are the physiological ligand), chemokines, and neurokinins (Table 1). However, the primary treatment options currently available for the management of allergy remain histamine H_1 -receptor antagonists, sympathomimetics (α and β), glucocorticosteroids (topical/systemic/intranasal/inhaled), and mast cell stabilizers (51). β -adrenoceptor agonists do not appear to target the allergy cascade or reduce chronic allergic inflammation *in vivo*, despite inhibitory effects on inflammatory cells *in vitro* (52). Rather, these and α -adrenoceptor agonists act on the downstream manifestations of allergic inflammation: bronchial hyperresponsiveness and nasal vascular congestion, respectively (52–54). Both mast cell stabilizers and glucocorticosteroids act by inhibiting the allergy cascade. However, glucocorticosteroids lack selectivity for the allergy cascade, exerting potent anti-inflammatory and immunosuppressive actions throughout the body via effects on leukocyte circulatory kinetics and function, and on inflammatory mediators (e.g. prostaglandins, histamine, leukotrienes, interleukins, interferon- γ , and tumour necrosis factor- α) (55). This may result in the well-known complications of glucocorticosteroid therapy.

The primary mechanism of action of H_1 -receptor antagonists in allergic diseases is to block the action of histamine at the H_1 -receptor. However, *in vitro* experiments have suggested that some histamine H_1 -receptor antagonists may exhibit additional mechanisms (56); for example, desloratadine inhibits the release or generation of inflammatory mediators by mast cells, basophils, and other cells (57). Leukotriene C_4 , prostaglandin D_2 , tryptase, granulocyte macrophage colony-stimulating factor (GM-CSF), RANTES induced by tumour necrosis factor- α , P-selectin and ICAM-1 induced by histamine,

Table 1 Newer treatment options, and products under development, that target specific inflammatory mediators

Target	Products	Allergy indications*
Fc ϵ R1	Anti-Fc ϵ R1 monoclonal antibody	Allergic rhinitis, asthma
Immunoglobulin E	Omalizumab (anti-IgE monoclonal antibody; Xolair)	Allergic rhinitis, asthma
Interleukin-4	Interleukin-4 receptor (Nuvance); others in development	Asthma
Interleukin-5	Mepolizumab, SCH 55700/CDP 835, and SB-240563 (anti-IL-5 monoclonal antibody)	Asthma
Integrin	SB-683698 (VLA4 integrin antagonist) and R411 (integrin antagonist); others	Asthma
Leukotriene	Zafirlukast and montelukast (leukotriene inhibitors; Accolate and Singulair)	Asthma
Neurokinin	SR-140333 and saredutant (neurokinin antagonists)	Asthma
Platelet-activating factor	Pafase (PAF-acetyl hydrolase)	Asthma

* Approved or proposed.

several interleukins (IL-1 β , IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, IL-18), and platelet-activating factor are among the mediators affected by desloratadine *in vitro*. Furthermore, *in vitro* studies revealed that desloratadine decreases the chemotaxis and activation of eosinophils and neutrophils and significantly down-regulates the expression of CD11b on polymorphonuclear leukocytes, suggesting inhibition of transmigration capacity (58). In atopic patients with SAR who were administered desloratadine 20 mg daily ($n=13$) for a week, supernatants of peripheral blood mononuclear cells (PBMCs) showed increased expression of interferon- γ (type 1 cytokine) and decreased expression of IL-4, IL-5, and IL-10 (type 2 cytokines), compared with supernatants of PBMCs of those administered placebo ($n=6$) (59). Also, desloratadine recipients had increased natural killer (NK) cell activity and decreased circulating basophils, eosinophils, and serum VCAM-1.

Efficacy against multiple disease manifestations of allergy

Given the systemic nature of allergy, targeting of the allergy cascade should result in efficacy against multiple disease manifestations. Desloratadine 5 mg once daily is effective in the treatment of both seasonal allergic rhinitis (SAR) and perennial allergic rhinitis. In people with SAR and symptoms of asthma, desloratadine relieves asthma symptoms and decreases the use of rescue medication. Desloratadine also relieves the symptoms of chronic idiopathic urticaria (CIU), 5 mg once daily being superior to placebo in controlling pruritus and total symptoms beginning with the first dose and throughout the 6 weeks of the study (Fig. 2) (60).

Desloratadine 5 mg once daily relieves the nasal and non-nasal symptoms of allergic rhinitis,

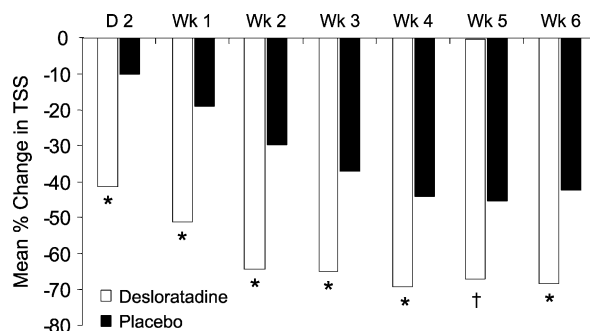


Figure 2 Desloratadine therapy in chronic idiopathic urticaria (CIU), as demonstrated in a double-blind, randomized, placebo-controlled, multicentre trial that included 190 patients aged 12 years and above with at least a 6-week history of CIU and experiencing a flare of at least moderate severity. Mean percentage reduction in total symptom score (TSS) from baseline. * $P < 0.001$; † $P = 0.002$. Reproduced with permission from (69).

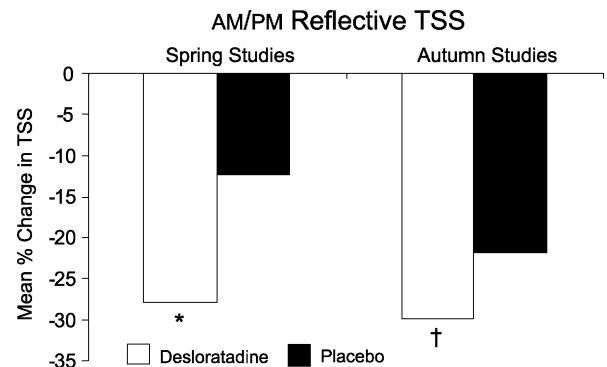


Figure 3 Desloratadine therapy in seasonal allergic rhinitis. Mean percentage reduction in morning/evening reflective total symptom score (TSS) from baseline. * $P < 0.01$; † $P = 0.02$. Adapted from (61).

both SAR and perennial allergic rhinitis. Two multicentre, randomized, double-blind, placebo-controlled, parallel-group investigations were conducted in patients with SAR, one during the spring allergy season (172 and 174 patients in the desloratadine and placebo groups, respectively) and one during the autumn allergy season (164 patients in each group) (61). Patients aged 12 years or older with a minimum 2-year history of SAR were randomized to desloratadine 5 mg or placebo once daily for 14 days, following a 3-day run-in period. Nasal symptoms (itching, stuffiness/congestion, rhinorrhoea, and sneezing) and non-nasal symptoms (itching or burning eyes, itching of ears or palate, eye redness, and tearing) reflective of the previous 12 h were scored in the morning and the evening. The primary efficacy assessment was the mean change from baseline in the total symptom score (TSS) averaged over the 2-week study period. The 28% (spring) and 30% (autumn) reduction in the TSS produced by desloratadine was significantly greater than the reduction produced by placebo (13% ($P < 0.01$) and 22% ($P = 0.02$), respectively) (Fig. 3). Similar results were obtained in the treatment of perennial allergic rhinitis, in which the 4-week average change in instantaneous TSS showed a significantly greater reduction from baseline with desloratadine treatment than with placebo ($P = 0.005$) (Fig. 4) (62).

In patients with SAR and mild-to-moderate asthma, desloratadine relieves symptoms of both conditions. Two multicentre, randomized, double-blind, placebo-controlled, parallel-group investigations were conducted in a total of 613 patients aged 15 years or older who had a minimum 2-year history of SAR and concomitant mild-to-moderate asthma that worsened during the autumn/winter allergy season (63). Participants had to have a prespecified severity of symptoms of SAR and asthma for 3 days

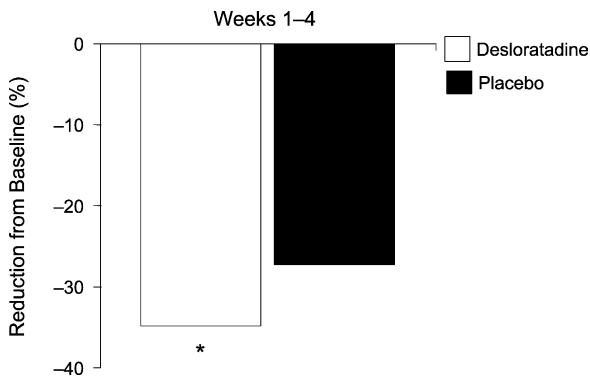


Figure 4 Desloratadine efficacy in perennial allergic rhinitis: mean percentage reduction in morning/evening instantaneous total symptom score (TSS) from baseline. * $P=0.005$. Adapted from (62,70).

before baseline assessment, a forced expiratory volume in 1 s (FEV_1) of at least 70% of predicted value, and asthma symptoms controlled by inhaled bronchodilators only. Patients were excluded if they used corticosteroids, antihistamines, decongestants, or more than 12 albuterol inhalations per day. Following a 3–4-day screening period, patients were randomized to desloratadine 5 mg or placebo once daily for 4 weeks. Symptoms from the previous 12 h were scored in the morning and the evening, including asthma symptoms (cough, wheeze, and difficulty breathing) and the nasal and non-nasal symptoms of SAR. Desloratadine recipients achieved a significantly greater decrease from baseline in the total asthma symptom score than placebo recipients during the first 2 weeks ($P=0.003$) and for the entire 4-week study period ($P=0.022$) (Fig. 5). The once-daily desloratadine regimen also reduced the use of albuterol to control asthma symptoms ($P \leq 0.003$ vs. placebo), while maintaining the FEV_1 .

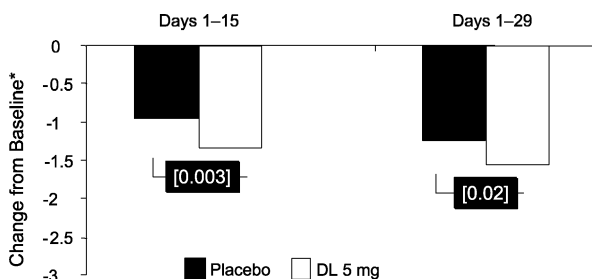


Figure 5 Desloratadine (DL) therapy in seasonal allergic rhinitis and concomitant asthma. Mean change from baseline in reflective total asthma symptom score from baseline. $P=0.003$ for the difference between desloratadine and placebo during days 1–15; $P=0.02$ for the difference between desloratadine and placebo during days 1–29. Adapted from (63).

Efficacy and safety: improved clinical profile

New treatment options should have superior safety with equivalent clinical benefits to existing therapies, or demonstrable additional benefits over existing therapies with no loss of safety. Unlike many existing second-generation H_1 -receptor antagonists, desloratadine provides the added benefit of efficacy against nasal obstruction.

Efficacy against nasal obstruction

Desloratadine once daily demonstrates activity against nasal obstruction (64), whether assessed subjectively as congestion and/or stuffiness scored over a range from 0 (none) to 3 (severe), or objectively as nasal airflow (in ml/s) measured by nasal rhinomanometry.

The efficacy of desloratadine was documented subjectively during the pollen season in patients with symptomatic SAR or with concurrent SAR and asthma in multicentre, double-blind, placebo-controlled studies (64,65). Three studies, each of which enrolled approximately 300 patients with symptomatic SAR, demonstrated relief of the symptom of nasal obstruction with administration of desloratadine 5 mg once daily (65). Symptoms were assessed twice daily, in the morning and the evening, and were reflective of the previous 12 h. The change from baseline was averaged over the study duration (either 2 or 4 weeks). Baseline scores ranged from 2.20 to 2.39, and desloratadine therapy resulted in a mean reduction in scores of 0.50–0.56 (21.3–23.5%). This effect was significant in comparison with the 0.35–0.40 (13.6–16.2%) mean reduction in the scores of the placebo groups ($P < 0.05$ for each study). In the studies of patients with history of 2 years or more of concurrent SAR and asthma, desloratadine 5 mg once daily produced significant relief of congestion after the first dose (64).

The efficacy of desloratadine was documented both objectively and subjectively outside of the pollen season in SAR patients exposed to an experimental allergen challenge in an environmental chamber. Three single-dose studies demonstrated the efficacy of desloratadine 5 mg in relieving subjectively documented nasal obstruction; administration of desloratadine after initial allergen challenge caused a greater change (improvement) from baseline than did placebo in the nasal obstruction symptom score ($P \leq 0.02$) (66). A subsequent placebo-controlled crossover study in 47 patients with SAR assessed the ability of desloratadine 5 mg once daily for 7 days to prevent nasal obstruction during exposure to artificially and strictly maintained levels of antigen throughout 6 h of testing outside of the regular pollen season (67). During allergen challenge, periodic assessment was made of objective nasal obstruction, nasal secretions,

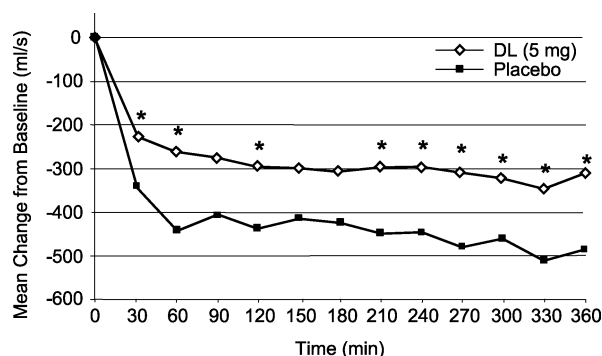


Figure 6 Mean change (decrease) from baseline nasal airflow (in ml/s) in response to allergen exposure after treatment with desloratadine 5 mg (DL) or placebo every morning for 7 days. *P* values refer to comparison between desloratadine and placebo. **P* = 0.005. From (67).

and nasal and non-nasal SAR symptom severity. Nasal obstruction was documented objectively as nasal airflow (mL/s), measured by active anterior rhinomanometry immediately before (baseline) and every 30 min during allergen exposure.

Desloratadine administration was associated with less decrease from baseline, as compared with placebo, in the mean nasal airflow at most assessment times (primary endpoint) and in the mean severity score for the symptom of nasal obstruction at all assessment times. Desloratadine administration was associated with significantly less severely decreased nasal airflow within 30 min of allergen exposure ($P < 0.02$), a benefit that continued throughout the 6-h period of allergen exposure (Fig. 6). With desloratadine, nasal secretions were also less ($P < 0.001$), and symptoms were less severe, including nasal congestion ($P < 0.002$), rhinorrhoea, and sneezing (67).

A systematic evaluation of double-blind, placebo-controlled studies assessed the effects of cetirizine, fexofenadine, loratadine, and desloratadine on nasal obstruction (68). Only studies that used clinically approved drug doses and specifically reported effects on nasal obstruction (congestion) were included. Placebo effects were factored out, and severity scores were standardized. Desloratadine was the only agent that consistently reduced nasal congestion greater than placebo in all studies analysed (Fig. 7).

Safety

Desloratadine is tolerated well (65). In controlled clinical studies, the rate of reported anticholinergic and sedative effects was similar to that with placebo. Also, there were no clinically significant abnormalities in electrocardiographic parameters, laboratory profiles, or vital signs.

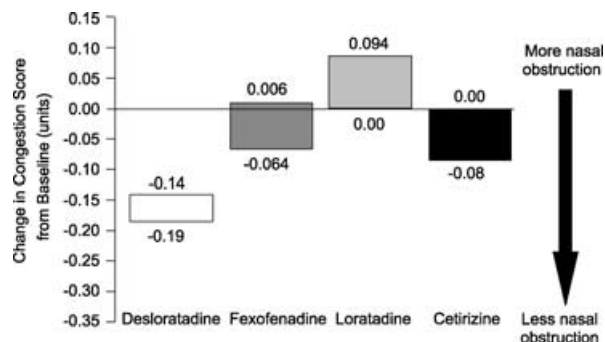


Figure 7 Systematic review of double-blind, placebo-controlled studies that examined the activity of second-generation histamine H_1 -receptor antagonists on nasal obstruction. Adapted from (68).

Improved quality-of-life measures

Given the burden of allergic diseases on psychosocial well being, one goal of treatment should be the improvement of quality of life. Desloratadine improves quality of life by decreasing the effect of allergic symptoms on sleep and daily activities. A multicentre, randomized, double-blind, placebo-controlled study of 190 patients with CIU of at least 6 weeks' duration determined that desloratadine 5 mg once daily improved both CIU-impaired sleep and CIU-impaired ability to conduct daily activities – an effect that was evident after the first dose and was maintained throughout the 6 weeks of the study ($P < 0.05$) (60). In a German postmarketing study of nearly 50 000 patients, SAR caused moderate or severe interference with daily activities in 40% of patients before desloratadine therapy, compared with only 3% during therapy. Similarly, before therapy 34.3% of patients experienced moderate or severe disruption of sleep, compared with only 2.6% during therapy (57).

Conclusions

Scientific, genetic, epidemiological, and pharmacoeconomic research has transformed our understanding of allergy. New endpoints for research and new therapeutic targets have become clear. Efficacy endpoints of antiallergy treatment are also changing. Ideally, new antiallergy therapies should intervene in the systemic allergic inflammatory cascade, with broad clinical efficacy in multiple allergic disease states, an improved clinical efficacy profile compared with existing therapies, and a positive impact on disease-impaired quality-of-life measures.

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