Rhinitis affects millions of people around the world, places a huge burden on the economy and reduces patients’ health-related quality of life. Azelastine nasal spray is a second-generation antihistamine, indicated for the treatment of allergic and nonallergic rhinitis in both adults and children. It offers a rapid onset of action (15 min) and flexibility of both dose (i.e., one or two sprays/nostril twice daily) as well as dosage (i.e., fixed or as needed). Compared with other agents used to treat allergic rhinitis, azelastine nasal spray exhibits superior efficacy to oral antihistamines (e.g., desloratadine and cetirizine), other intranasal antihistamines (e.g., levocabastine) and the intranasal corticosteroid mometasone furoate, and comparable efficacy to the potent intranasal corticosteroid fluticasone propionate (FP). Combination therapy with intranasal FP has the potential to enhance clinical benefit, as the combination of azelastine and FP nasal sprays reduce symptoms in allergic rhinitis patients more than either agent alone. Azelastine nasal spray has an excellent safety profile.

**Keywords:** allergic rhinitis • azelastine nasal spray • intranasal corticosteroid • nonallergic rhinitis • oral antihistamine

Rhinitis is an inflammatory disease of the nasal mucosa affecting approximately 10–30% of adults and 40% of children, making it the sixth most common chronic illness in the USA. Over the past 30 years, the prevalence of this condition has risen dramatically in industrialized countries, with England, Sweden and Australia reporting a doubling in rates, a trend similar to that seen with other atopic conditions such as asthma. Rhinitis places a huge burden on the economy, being responsible for between US$2 and 5 billion annually in both direct and indirect costs [1], and approximately 3.5 million lost work days per year [2].

Traditionally, rhinitis has been classified as allergic, nonallergic and mixed. Definitions of these rhinitis classifications are discussed later. Patients with seasonal allergic rhinitis (SAR) present with a huge range of symptoms, including nasal congestion, runny nose, nasal and nasopharyngeal itching, ear symptoms, sneezing, and ocular symptoms in many patients, including itchy and watery eyes [3]. The symptoms of sneezing, itching and rhinorrhea are less common with perennial rhinitis (PR).

Rhinitis symptoms have a major negative impact on patients’ health-related quality of life (HRQoL). They impair not only patients’ daily activities, but furthermore disturb quality of sleep, which causes fatigue during the day and impairs cognitive function [4]. An inability to concentrate is a frequent complaint made by rhinitis sufferers, and in the case of SAR, patients often avoid outdoor activities to avoid allergen exposure. The Joint Task Force on Allergy Practice and Parameters mentions that improving the negative impact on daily life in rhinitis patients defines successful treatment as much as providing symptom relief.

A recent survey investigated symptom perception and the impact of allergic rhinitis (AR) in 447 patients and their doctors on HRQoL [5]. The results highlighted the high symptom burden and impaired HRQoL associated with AR. Interestingly, patients rated their disease as more severe than physicians did. At the time of the consultation, 44% of patients were suffering from nasal and ocular symptoms, 23.7% of patients reported that their current nasal and ocular symptoms were moderate or severe in nature, and approximately two-thirds of patients with intermittent disease reported some impairment of their professional or daily life as a result of AR [5]. HRQoL correlated negatively with the number of symptoms, with AR having a
significantly greater impact on patients with more persistent disease compared with those with intermittent disease. Finally, more than 50% of patients surveyed were using two or more medications for their AR [5]. AR seems to be a disease that is poorly controlled and whose effects are underestimated.

**Traditional classification of rhinitis**

Traditionally, rhinitis has been classified as allergic, nonallergic or mixed (Figure 1) [6]. With AR, symptoms occur in association with a specific IgE-mediated response. With nonallergic rhinitis, symptoms are induced by irritant triggers but without an IgE-mediated response. AR is further classified as seasonal or perennial. SAR symptoms are induced by exposure to pollens, whilst PR is associated with environmental allergens that are generally present on a year-round basis.

As many as half of all patients diagnosed with rhinitis have nonallergic disease. Nonallergic rhinitis includes infectious rhinitis (also known as rhinosinusitis), occupational rhinitis, drug-induced rhinitis (e.g., rhinitis induced by aspirin and nonsteroidal anti-inflammatory drugs [NSAIDs]), hormonal rhinitis (e.g., during pregnancy), rhinitis in smokers, food-induced rhinitis (very rare), nonallergic rhinitis with eosinophilia and eosinophilic rhinitis, senile rhinitis, atrophic rhinitis (often infected with *Klebsiella ozaenae*) and finally idiopathic rhinitis. Details of diagnosis and management of rhinitis are provided in the Allergic Rhinitis and its Impact on Asthma (ARIA) report [8–10], and the updated American Association of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology practice parameter [7].

**New AR classification**

The classification of AR into ‘seasonal’ and ‘perennial’ categories is not entirely satisfactory. The majority of AR patients are sensitized to many different allergens and are exposed throughout the year [8–10]. In many patients, perennial symptoms are often present, and patients experience seasonal exacerbations when exposed to pollens or molds. Therefore, the old classification of AR into seasonal and perennial categories is not indicative of the real-life situation. A major change in the subdivision of AR was proposed by ARIA (Figure 2). AR is subdivided into ‘intermittent’ and ‘persistent’ disease, and the severity classified as either ‘mild’ or ‘moderate/severe’. However, it is important to remember that indications for treatment and clinical studies investigating the efficacy of azelastine still refer to the older rhinitis classification.

**Treatment guidelines**

As many as 66% of adult allergy sufferers are dissatisfied with their current allergy medication due to a lack of effectiveness [11]. Clearly, effective and convenient therapies with a good safety profile are needed to treat patients with AR. The ARIA guidelines recommend a stepwise approach to therapy based upon the frequency and severity of symptoms (Table 1). Intranasal antihistamines are recommended for all severities of intermittent rhinitis symptoms and mild persistent symptoms. Treatment guidelines from the Joint Task Force and the WHO agree with ARIA, and recommend antihistamines (both topical and oral second-generation) be used as a first-line therapy for AR. Intranasal corticosteroids may also be considered as initial therapy for AR patients with more severe or persistent symptoms, particularly nasal congestion.

**Azelastine**

Azelastine hydrochloride nasal spray is a topically administered second-generation antihistamine, marketed as Allergodil® (Meda AB, Stockholm, Sweden) in Europe and Astelin® (Meda Pharmaceuticals Inc., NJ, USA) in the USA. It is indicated for the treatment of the symptoms of SAR (approved in 1996) such as rhinorrhea, sneezing, and nasal pruritus in adults and children 5 years of age and older. It is also indicated for the treatment of the symptoms of vasomotor rhinitis (VMR; approved in 1999) such as rhinorrhea, nasal congestion and postnasal drip in adults and children aged 12 years or older. The recommended dose of azelastine nasal spray depends on patient age. For those aged 12 years or older, two sprays per nostril twice daily is recommended, which reduces to one spray per nostril twice daily in children aged 5–11 years. A new formulation of azelastine nasal spray with sucralose as a taste-masking agent (Astepro®) was approved in the USA in October 2008 for the treatment of SAR in patients 12 years of age and older.

Applying azelastine topically to the nasal mucosa means that the drug is delivered directly to the site of inflammation, where it is needed most. Compared with systemic treatments, higher concentrations of azelastine can be applied topically, which should enhance its anti-allergic and anti-inflammatory effects. In addition, the risk of interaction with concomitant medication, and the potential for systemic adverse effects is reduced.

![Figure 1. Traditional classification of rhinitis. VMR: Vasomotor rhinitis.](image-url)
Azelastine nasal spray for the treatment of allergic & nonallergic rhinitis

Drug Profile

events is minimized. The efficacy and safety of azelastine nasal spray in treating AR and nonallergic rhinitis have been determined in a number of US multicenter, randomized, double-blind, placebo-controlled trials. In all trials, azelastine was associated with a rapid onset of action, and a sustained improvement over time in rhinitis, congestion, and other symptoms [12]. The topical application of azelastine nasal spray has been shown to be effective in treating rhinitis patients who remained at least moderately symptomatic after therapy with either oral loratadine (Claritin®, Schering Plough, USA) or fexofenadine (Allegra®, Sanofi Aventis, USA) [13,14].

Dosage
A dosage of two sprays per nostril twicely daily improves not only all symptoms of allergic and nonallergic rhinitis, as shown in an open trial with 4000 patients [15], but also HRQoL [16] immediately.

Table 1. Summary of ARIA allergic rhinitis management guidelines.

<table>
<thead>
<tr>
<th>Rhinitis severity</th>
<th>ARIA recommendation</th>
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<tbody>
<tr>
<td>Mild intermittent</td>
<td>Oral/intranasal antihistamines and/or decongestants</td>
</tr>
<tr>
<td>Moderate/severe intermittent</td>
<td>Oral antihistamines and/or decongestants, intranasal antihistamines, intranasal corticosteroids or cromones</td>
</tr>
</tbody>
</table>
| Mild persistent                    | Oral antihistamines and/or decongestants, intranasal antihistamines, intranasal corticosteroids or cromones  
                                        | A step-wise approach is advised with reassessment after 2 weeks. If symptoms are controlled and the patient is receiving an intranasal corticosteroid, the dose should be reduced, but otherwise treatment continued. If symptoms persist and the patient is receiving antihistamines or cromones, a change should be made to an intranasal corticosteroid |
| Moderate/severe persistent        | Intranasal corticosteroid (first-line treatment)                                    |
|                                   | If symptoms are uncontrolled after 2–4 weeks, medication should be added depending on the persistent symptom. For example, add an antihistamine if the major symptom is rhinorrhea, pruritis or sneezing, double the dose of intranasal steroid for persistent nasal blockage and add ipratropium for prominent complaint of rhinorrhea |

ARIA: Allergic Rhinitis and its Impact on Asthma.
Azelastine nasal spray at a dosage of one spray per nostril twice daily is also effective and has an improved tolerability profile compared with two sprays per nostril twice daily in patients (≥212 years; n = 554) with moderate-to-severe SAR [17]. In addition, one spray per nostril twice daily of azelastine was associated with significant improvements in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) daily activity and nasal symptoms domains and patient global evaluations compared with placebo. The incidence of a bitter aftertaste following azelastine application more than halved, and the incidence of somnolence was decreased almost 30-times in the one-spray group versus the labeled incidence with the two-spray regimen.

As needed
Azelastine nasal spray can also be used on an as-needed basis by virtue of its rapid onset of action, just 15 min after application [18]. Ciprandi and colleagues carried out a randomized, controlled study in 30 patients sensitized to *Parietaria* pollen and grass and treated them with azelastine (0.56 or 0.28 mg/day), or as needed [19]. Patients who received the 0.56- or 0.28-mg/day dose had a marked improvement in their rhinitis symptoms, and a concomitant reduction in markers of inflammation, most notably neutrophil and eosinophil counts and intracellular adhesion molecule (ICAM)-1 expression in nasal scrapings. Although this anti-inflammatory effect was absent in patients treated with azelastine nasal spray on an as-needed basis, these patients did show an improvement in their rhinitis symptoms [19]. Therefore, although patients derive maximum benefit from regular treatment with azelastine, as-needed therapy may be useful in the treatment of clinical symptoms and would be expected to improve drug tolerability and patient compliance.

Chemistry
The chemical name of azelastine hydrochloride is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-monohydrochloride. Its empirical formula and molecular weight are C_{22}H_{24}ClN_{2}O.HCl and 418.37, respectively, and structurally it is arranged as a seven-membered ring (Figure 3).

Azelastine is a white, almost odorless crystal with a bitter taste. It is soluble in dichloromethane and chloroform, sparingly soluble in propylene glycol and methanol, slightly soluble in glycerin, octanol and ethanol, and almost insoluble in hexane.

Pharmacokinetics & metabolism
The systemic bioavailability of intranasally administered azelastine hydrochloride is approximately 40%, with maximum plasma concentrations (C_{max}) observed within 2–3 h. Based on intravenous and oral administration, the elimination half-life is 22 h, steady-state volume of distribution is 14.5 l/kg and plasma clearance is 0.5 l/h/kg, respectively. *In vitro* studies with human plasma indicate plasma protein binding of azelastine and desmethylazelastine of approximately 88 and 97%, respectively. Azelastine is oxidatively metabolized by the cytochrome P450 enzyme system into a principally active metabolite, desmethyazelastine and two inactive carboxylic acid metabolites. When azelastine is administered orally, desmethylazelastine has an elimination half-life ranging from 22 to 54 h. Approximately 75% of an oral dose of radiolabeled azelastine is excreted with feces, with less than 10% excreted unchanged.

Following oral administration, pharmacokinetic parameters of azelastine are not influenced by age, gender or hepatic impairment. However, oral, single-dose studies show that patients with renal insufficiency (i.e., creatinine clearance <50 ml/min) had a 70–75% higher C_{max} and AUC compared with normal subjects, but time to C_{max} remained the same.

Mode of action
Azelastine has a fast and long-lasting effect due to its complex anti-inflammatory mode of action [6,20]. It is a high-affinity histamine H_{1}-receptor antagonist, being ten-times more potent than chlorpheniramine, and also has some affinity for H_{2} receptors. In a VCC trial, azelastine showed one of the fastest onsets of action (15 min with nasal spray) [18] among the currently available rhinitis medications, and its effect lasts at least 12 h, thus allowing for a once- or twice-daily dosing regimen.

Azelastine’s anti-inflammatory activity is widespread. Azelastine inhibits TNF-α release, granulocyte macrophage colony-stimulating factor generation and reduces the number of a range of inflammatory cytokines, including IL-1β, IL-4, IL-6 and IL-8 [6,20]. These cytokines perpetuate the inflammatory response [21]. *In vitro* azelastine decreases free-radical production by human eosinophils and neutrophils, and calcium influx induced by platelet-activating factor. It reduces inflammatory cell migration in patients with rhinitis, most likely as a consequence of the downregulation of ICAM-1 expression [6,20], and inhibits kinin (e.g., bradykinin and substance P), platelet-activating factor and leukotriene release *in vitro* and *in vivo*. Leukotrienes are associated with dilation of vessels, increased vascular permeability and edema, which results in nasal congestion, mucus production and recruitment of inflammatory cells *in vitro* [22] and *in vivo* [21]. Clinically, substance P and bradykinin are associated with the AR symptoms of nasal itching and sneezing, but may also contribute to the onset of nonallergic rhinitis symptoms.

The widespread anti-inflammatory effects of azelastine ensure that it is a highly effective treatment, combating the broad range of clinical symptoms associated with rhinitis.

Clinical efficacy of azelastine
The clinical efficacy of azelastine nasal spray has been confirmed in a real-world setting for the treatment of allergic, mixed and
nonallergic rhinitis [15]. A total of 4364 patients were treated with azelastine nasal spray (two sprays per nostril twice daily) for 2 weeks. Overall, 90% of SAR patients reported some or complete control of the symptom of sneezing and 78% of VMR patients reported an improvement in their postnasal drip. Of patients reporting sleep difficulties or impaired daytime activities owing to rhinitis symptoms, 85% experienced improvements in these parameters with azelastine therapy.

Comparisons with other agents used to treat AR

Allergic rhinitis is a disease with a complex pathophysiology. Therefore, several classes of drugs are available to treat it: oral antihistamines (e.g., desloratadine [Clarinex®, Schering Plough, USA] and cetirizine [Zyrtec®, Pfizer, USA]), intranasal corticosteroids (e.g., fluticasone propionate [Flonase®, GSK, USA] and mometasone furoate [Nasonex®, Schering Plough, USA]), intranasal mast cell stabilizers (e.g., nedocromil [Tilade®, King Pharmaceuticals, USA] and cromoglycate [Chromohexal®, Hexal Pharma, South Africa]), as well as other intranasal antihistamines (e.g., levocabastine [Livostin®, Jansen-Cilag, NJ, USA]).

The number needed to treat (NNT) estimates the number of patients that must be treated with a particular drug in order to have one positive outcome. As such, it is a useful tool to compare the efficacy of treatments available for the treatment of rhinitis. It is preferable for a drug to have a low NNT, as less patients would need to be treated before one positive outcome occurred. Limited evidence due to the usage of only a single trial for each drug was reported by Portnoy and colleagues, estimating the NNT ranges as 5–6.3 for azelastine, 3–6 for intranasal corticosteroids and 4.6 for immunotherapy, compared with 9–35 for oral antihistamines [23].

A more recent meta-analysis systematically reviewed 21 separate publications examining the efficacy of azelastine nasal spray compared with other intranasal treatments (e.g., beclomethasone [Beconase®, GSK, USA] and budesonide [Rhinocort®, AstraZeneca, USA]), and levocabastine and oral preparations (e.g., loratadine, terfenadine [Seldane®, Sanofi Aventis, USA], cetirizine and ebastine [Kestine®, Pharmcare, USA]) [24]. The results showed that azelastine was more efficacious than placebo with a summary NNT of 5.0 but there was no statistical difference between the efficacy of azelastine nasal spray and any of the active comparators [24]. However, when the analysis was limited to studies in which an oral allergy treatment was the comparator, the point estimate of the pooled results favoured azelastine nasal spray (Figure 4). The results were consistent across SAR and nonallergic rhinitis, and across trials of different durations.

### Azelastine versus oral antihistamines

Azelastine nasal spray is more effective and has a more rapid onset of action compared with oral antihistamines in the treatment of AR [16–24], and is effective in those AR patients who had an inadequate response to oral antihistamine therapy [13,14]. In addition, azelastine nasal spray significantly reduces nasal congestion, a particularly bothersome symptom for rhinitis sufferers, without causing a sedative effect.

### Azelastine versus desloratadine

Desloratadine is a new, third-generation antihistamine tablet, which, unlike its second-generation counterparts, is thought to reduce nasal congestion, be non-sedating and not cause cardiac side effects. However, azelastine nasal spray (one spray per nostril) has been shown to be significantly better than desloratadine tablets (5 mg) in reducing the symptoms of SAR, including congestion, induced by allergen challenge in the Vienna Challenge Chamber (Figure 5) [18]. However, azelastine nasal spray and desloratadine tablets both significantly (p < 0.001) reduced nasal symptoms compared with placebo. Azelastine nasal spray was also superior to desloratadine tablets in alleviating nasal congestion, an unexpected result since second-generation antihistamines have little decongestant activity.

Furthermore, Azelastine nasal spray showed a much more rapid onset of action compared with desloratadine tablets (15 vs 150 min). Almost three-quarters of patients rated azelastine as at least ‘satisfactory’ compared with 55.6% for desloratadine and just 24.4% for placebo [18]. Others have confirmed this rapid onset of action of azelastine nasal spray [27]. The slow onset of action of

### Table: Author NNT (95% CI)

<table>
<thead>
<tr>
<th>Author</th>
<th>NNT (95% CI)</th>
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<tbody>
<tr>
<td>Passali</td>
<td>250 (9.1 to to 8.3)</td>
</tr>
<tr>
<td>Gambardelle</td>
<td>14.3 (2.6 to to 3.8)</td>
</tr>
<tr>
<td>Conde Hernandez</td>
<td>7.1 (2.7 to to 12.5)</td>
</tr>
<tr>
<td>Gastpar</td>
<td>10,000 (8.3 to to 8.3)</td>
</tr>
<tr>
<td>Gastpar</td>
<td>14.3 (4.2 to to 10)</td>
</tr>
<tr>
<td>Charpin</td>
<td>5 (2 to to 11.1)</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>20 (8.3 to to 50)</td>
</tr>
</tbody>
</table>

Fixed effects model; no significant heterogeneity

![Figure 4. Number needed to treat: a global assessment of efficacy as an outcome for azelastine nasal spray compared with oral agents for the treatment of allergic rhinitis.](image)
Azelastine versus cetirizine

Cetirizine hydrochloride is an oral, second-generation antihistamine indicated for the treatment of both SAR and perennial AR. Corren et al. examined the effectiveness and tolerability of azelastine (two sprays per nostril) and cetirizine tablets (10 mg once daily) over a period of 2 weeks in 307 patients with moderate-to-severe SAR [25]. Compared with cetirizine, azelastine nasal spray significantly (p = 0.015) improved nasal symptoms and patients’ HRQoL (p = 0.049) as assessed by the RQLQ [25]. In a second study with identical methodology, azelastine improved the nasal symptoms, with a significant improvement observed for nasal congestion (p = 0.049) and sneezing (p = 0.01) [28], as well as HRQoL (p = 0.002), compared with cetirizine [28]. Pooled data of both trials showed significant results for all nasal symptoms [26].

The positive effect of azelastine nasal spray on congestion was observed, despite the fact that the cetirizine group had the added benefit of daily use of a placebo saline spray [28].

The effect on nasal congestion is an important property of azelastine nasal spray; in a large open-label trial of 4000 patients with SAR, nasal congestion was reported as the most bothersome rhinitis symptom by 52% of patients [18].

Impairment of HRQoL is a major complaint of rhinitis sufferers. Results from two 2-week studies showed that azelastine nasal spray (two sprays per nostril twice daily) was significantly superior to oral cetirizine (10 mg) in terms of improvement in overall RQLQ score (p < 0.05) [16]. A combined analysis of both studies confirmed the significant superiority of azelastine spray both in terms of the overall RQLQ score (p < 0.001) as well as each of the RQLQ domain scores (p < 0.03), including the nasal symptoms domain (p < 0.001). Berger and colleagues produced similar results (Figure 6) [28].

Nonresponders

As many as 20% of all AR patients do not respond to oral H1 blockers at all [14]. These nonresponders have been shown to be sensitive to therapy with azelastine nasal spray. For example, patients with moderate-to-severe AR who had a suboptimal response to loratadine showed significant symptom improvement following treatment with azelastine monotherapy or azelastine plus loratadine compared with placebo (p < 0.001) [14]. Another study showed similar results in patients who had an inadequate response to fexofenadine treatment for 1 week [18]. Therefore, monotherapy with azelastine nasal spray may be a useful treatment option in patients who have developed resistance to prior oral antihistamine therapy [20].

Azelastine versus intranasal corticosteroids

Azelastine nasal spray has many advantages over intranasal corticosteroids, despite having a weaker anti-inflammatory effect. It has a faster onset of action [27], whereas intranasal corticosteroids develop a maximum benefit over days or even weeks [21], necessitating the need to begin treatment before the onset of symptoms in order to obtain optimal benefit from therapy. Furthermore, a better safety profile is given for local application forms [27,28].

Azelastine versus fluticasone propionate

In a study with both allergic and nonallergic rhinitis sufferers, azelastine nasal spray (two sprays per nostril twice daily; 1.1 mg) showed comparable efficacy to fluticasone propionate nasal spray (two sprays per nostril daily; 200 µg) in improving patients’ RQLQ scores (Figure 7) and rhinitis symptoms [29]. Additional effects can be reached with a combination of azelastine and intranasal fluticasone propionate [30,31]. Ratner, for example, reported that the combination of both substances improved nasal symptoms by 37.9% compared with 27.1 and 24.8% with fluticasone and azelastine nasal spray, respectively (p < 0.05 vs either agent alone) [30].

Azelastine versus mometasone furoate

The fast onset of action of azelastine is also shown when compared with mometasone furoate, a modern nasal steroid with an onset of 12–72 h. An environmental exposure chamber trial showed no effect of the steroid on nasal symptoms within the

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**Figure 5. Major nasal symptom scores averaged over treatment and time for the per protocol population following administration of azelastine (one spray per nostril), desloratadine (5 mg) or placebo in patients with seasonal allergic rhinitis.**

Reprinted with permission from [18].
first 8 h after intake [27], whereas the benefit of azelastine was seen within 15 min and persisted at each time point throughout the 8-h allergen challenge.

**Azelastine versus intranasal mast cell stabilizers**

Mast cell stabilizers (e.g., nedocromil and cromoglycate), as the name suggests, block the release of mediators from mast cells. They are most frequently used when other drugs, such as antihistamines or topical corticosteroids, are ineffective or not well tolerated. Frequent dosing (three-to-six-times per day) is required for improvement of allergy symptoms and patients need to begin treatment before allergen contact [32]. In general, symptoms are reduced within 3–7 days of daily use, but the full effect may not be seen for 2–4 weeks. However, owing to the favorable safety profile, mast cell stabilizers are recommended for young children, pregnant women and the elderly for the treatment of allergy symptoms. Cromolyn sodium (4%) nasal solution (one spray per nostril every 4–6 h for 2 weeks) was superior to placebo in controlling allergy symptoms, providing overall symptom relief, and relieving sneezing and nasal congestion in self-selected patients with AR [33]. However, disodium cromoglycate (5.6 mg four-times daily) was inferior to the intranasal corticosteroid mometasone furoate in the treatment of SAR in terms of nasal symptom relief, improvement in nasal inspiratory flow, global evaluation of efficacy and reduction in eosinophil cationic protein concentration [34].

**Azelastine versus intranasal levocabastine**

Levocabastine is a potent and selective histamine H\textsubscript{1}-receptor antagonist. It has been shown to reduce a hyper-reactive response after nasal provocation with hypotonic aerosol in patients with AR [35]. The efficacy and tolerability of levocabastine and azelastine nasal spray was compared in a 4-week study in 180 patients suffering from AR. Azelastine nasal spray (1.12 mg, two sprays twice daily) was significantly superior at reducing both morning and evening nasal symptoms compared with levocabastine (0.4 mg, two sprays twice daily; \( p < 0.001 \)) [36]. Global efficacy was indicated very good or good by 90% of doctors and 92% of patients, respectively, for azelastine and 74% of doctors and 76% of patients, respectively, for levocabastine.

**Safety & tolerability**

Drugs delivered intranasally have a lower risk of causing systemic side effects and interacting with other drugs [37]. NDA studies have shown that azelastine nasal spray is safe and well tolerated for up to 4 weeks’ treatment in both adults and children.

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Figure 6. Mean improvement from baseline to day 14 in overall RQLQ score and individual RQLQ domain scores (intention-to-treat population). *\( p \leq 0.05 \) vs cetirizine; ‡\( p < 0.01 \) vs cetirizine.

RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire.

Reprinted with permission from [28].
(≥12 years) [38–42]. Bitter taste, headache, somnolence and nasal burning were the most frequently reported adverse events; however, the vast majority of these were either mild or moderate in severity. It is worth noting that slightly tilting the head forward and not inhaling the medication too deeply prevents deposition of drug in the nasopharynx, so reducing the problem of bitter taste. Similar degrees of somnolence (~2%) have been reported in both local azelastine and placebo groups in postmarketing surveillance studies [14,15,25,28]. The lower incidence of azelastine-related adverse events seen in these later trials is most likely due to correct dosing technique (i.e., head tilted forward and no deep inhalation), which would reduce systemic absorption, and hence also reduce bitter taste and somnolence. However, as the earlier NDA studies did show an increased incidence of somnolence whilst using azelastine nasal spray versus placebo, US prescribing recommendations warn against the concurrent use of alcohol and/or other CNS suppressants. To date, there have been no studies designed to specifically assess the effects of azelastine nasal spray on the CNS in humans. Data on oral azelastine describe occasional tiredness, and minimal effects on performance and vigilance with a dose of 2 mg/day [43].

Expert commentary
Intranasal antihistamines are recommended as a first-line therapy for AR. The intranasal mode of delivery is beneficial in several ways. First, it deposits the drug directly onto the nasal mucosa, delivering medication directly to the site(s) of inflammation and at concentrations much greater than that achievable with systemic drugs. Second, with topical application, the risk of interaction with concomitant medication and the potential for systemic adverse events are minimized. However, the activity is reduced to the target organ and has no input in reducing the general allergic inflammation.

Azelastine nasal spray is a second-generation antihistamine with a complex anti-inflammatory mode of action. Its anti-inflammatory effects are widespread, making it particularly suitable for the treatment of a complex inflammatory disorder such as rhinitis. It has proven efficacy in treating both allergic and nonallergic rhinitis, and is the only prescription antihistamine approved in the USA for the treatment of both SAR (1996) and nonallergic rhinitis (1999).

It has one of the fastest onsets of action (15 min for nasal spray) [18] among the currently available rhinitis medications, and its effects last at least 12 h, thus allowing for a once- or twice-daily dosing regimen.

Azelastine nasal spray offers flexibility of dosage. At a dosage of one spray per nostril twice daily, it has been shown to be effective, with an improved tolerability profile compared with two sprays per nostril twice daily in patients with moderate-to-severe SAR. The option of a one- or two-spray azelastine dosing regimen enables physicians to tailor treatment regimens to the individual patient. The choice of azelastine nasal spray dosage should be based on the severity and persistence of symptoms, as well as the patient’s acceptance of the nasal spray [6]. The two-spray dose could be used as the starting dose for patients with severe symptoms, and either maintained or tapered to the one-spray dose as required. The one-spray dose could be used as a starting dose in patients with mild-to-moderate symptoms, and if necessary the dose increased to two sprays per nostril twice daily if symptom control proved to be inadequate [17].

Azelastine nasal spray can also be used on an as-needed basis by virtue of its rapid onset of action. Patients treated with as-needed azelastine nasal spray show improvement in their rhinitis symptoms but without the concomitant reduction in markers of inflammation seen with fixed dosing [19]. As-needed therapy may reduce the bitter taste and somnolence sometimes associated with azelastine use and may improve patient compliance.
Compared with other agents used to treat AR, azelastine nasal spray is more effective than oral antihistamines and intranasal levocabastine with comparable efficacy to intranasal fluticasone propionate. Combination therapy with intranasal corticosteroids has provided some interesting results and has the potential to enhance clinical benefit.

**Five-year view**

The economic situation may influence the use of drugs in nonserious diseases in the next few years: whereas both H1-receptor antagonists or topical steroids are recommended as first-line treatment in AR, antihistamines are cheaper. For the same reason, combination therapies of oral antihistamines and nasal corticosteroids will hardly become market standard, despite their good pharmacological profile. Therefore, topically used antihistamines like azelastine will gain in importance, especially used on demand for moderate symptoms.

The therapeutic power of H1-receptor antagonists is limited, especially if they have no activity on other pathways of the allergic inflammation process, such as azelastine. Therefore, it is still impossible to eliminate severe symptoms with this class of drugs and this will not change. That is the reason why several other compounds are in development with very different modes of action. Some of these are even linked to cancer treatment. However, there is no light at the end of the tunnel within the next 5 years.

The improvement of specific immunotherapy in terms of tolerability and efficacy will lead to a more frequent use. Comedication of topically used antihistamines on demand will support immunotherapy in a beneficial manner.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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**References**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


- Important review, which sourced publications from 1995 to 2007 regarding the treatment of allergic and vasomotor rhinitis. It concluded that intranasal antihistamine therapy is an effective mode
of drug delivery in patients with allergic and vasomotor rhinitis, particularly if rapid symptom relief is required, or if congestion is a major symptom.

Combination therapy with azelastine and nasal corticosteroids may also be an effective treatment strategy.


**Important publication showing that azelastine nasal spray controlled all rhinitis symptoms, including nasal congestion, in patients with allergic rhinitis, vasomotor rhinitis and mixed rhinitis.**


**Demonstrated that azelastine nasal spray at a dose of one spray per nostril twice daily is effective and has improved tolerability compared with double the dose in patients with seasonal allergic rhinitis (SAR). This means that the azelastine dose can be tailored to suit individual patient needs, without compromising clinical efficacy.**


**Demonstrated that on-demand use of azelastine nasal spray achieved acceptable clinical control of rhinitis symptoms but did not significantly reduce allergic inflammation, as observed at doses of 0.28 mg/day and 0.56 mg/day. These data emphasize the flexibility of azelastine nasal spray as a treatment modality for allergic rhinitis and has important implications for patient compliance.**


**Demonstrated that combination therapy with azelastine and fluticasone propionate nasal sprays may provide a substantial therapeutic benefit for patients with SAR compared with therapy with either agent alone.**


**Demonstrated that combination therapy with azelastine and fluticasone propionate nasal sprays may provide a substantial therapeutic benefit for patients with SAR compared with therapy with either agent alone.**


Azelastine nasal spray for the treatment of allergic & nonallergic rhinitis

**Drug Profile**


**Website**


- Provides all relevant publications concerning allergy rhinitis and asthma.

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