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®, Pharmacare, 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 [16,17,24–26], 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 nonsedating 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

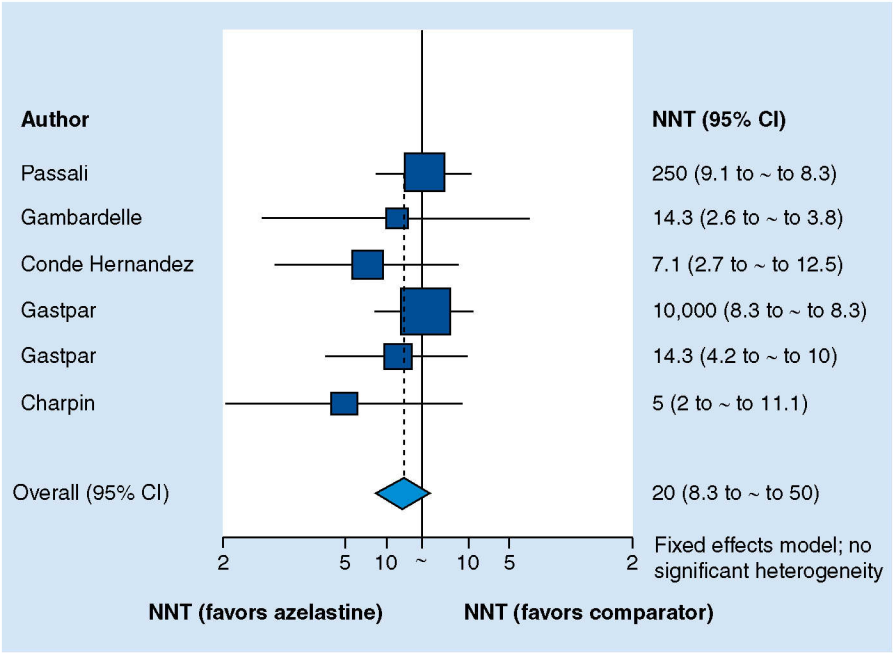

Figure 4. Number needed to treat: a global assessment of efficacy as an outcome for azelastine nasal spray compared with oral agents for the treatment of allergic rhinitis.
~: Crossing the middle line between favoring azelastine-favoring comparator; CI: Confidence interval; NNT: Number needed to treat.
Reprinted with permission from [24].

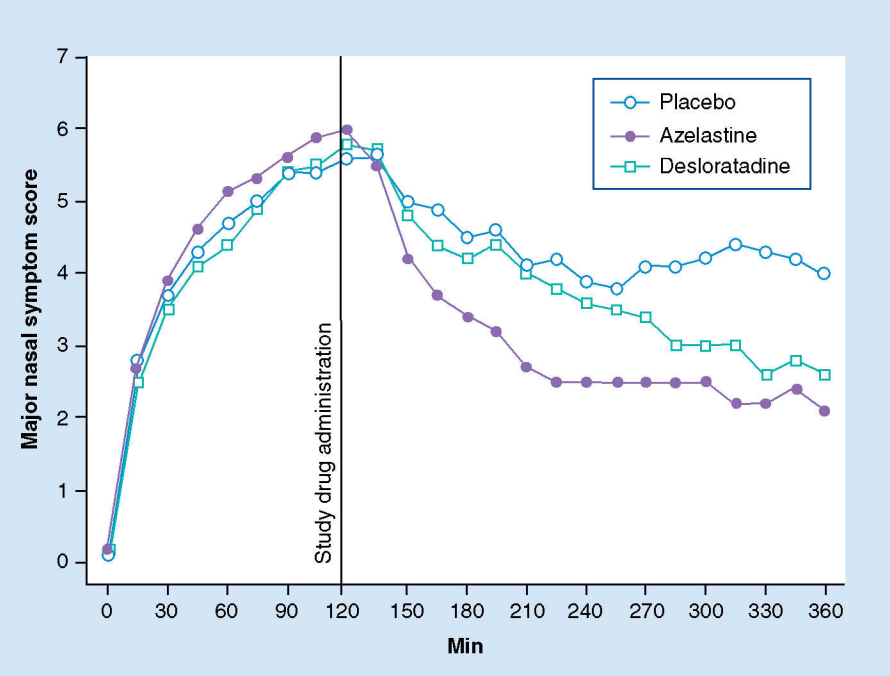

Figure 5. Major nasal symptom scores averaged over treatment and time for the per protocol population following administration of azelastine (one spray per nostril), desloratadine (5 mg) or placebo in patients with seasonal allergic rhinitis.
Reprinted with permission from [18].

desloratadine reported by Horak and colleagues may have been due to the encapsulation of the tablets for the purpose of study blinding, and/or due to the fact that symptoms were allowed to develop for 2 h before study medication was delivered [18].

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 [15].

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 H_1 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 [15]. 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

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_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

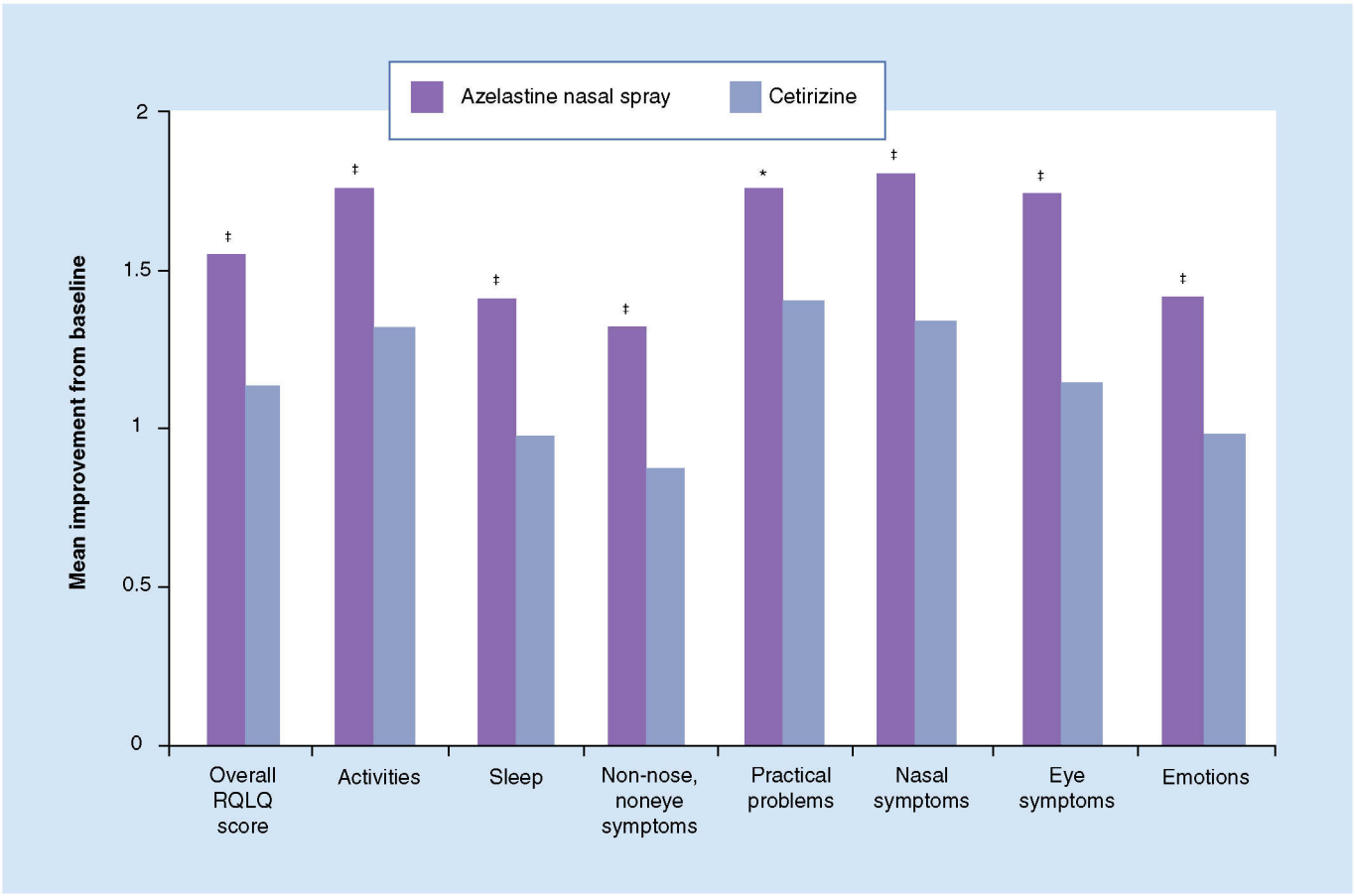

Figure 6. Mean improvement from baseline to day 14 in overall RQLQ score and individual RQLQ domain scores (intention-to-treat population). *$p \leq 0.05$ vs cetirizine; ‡$p < 0.01$ vs cetirizine.
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire.
Reprinted with permission from [28].

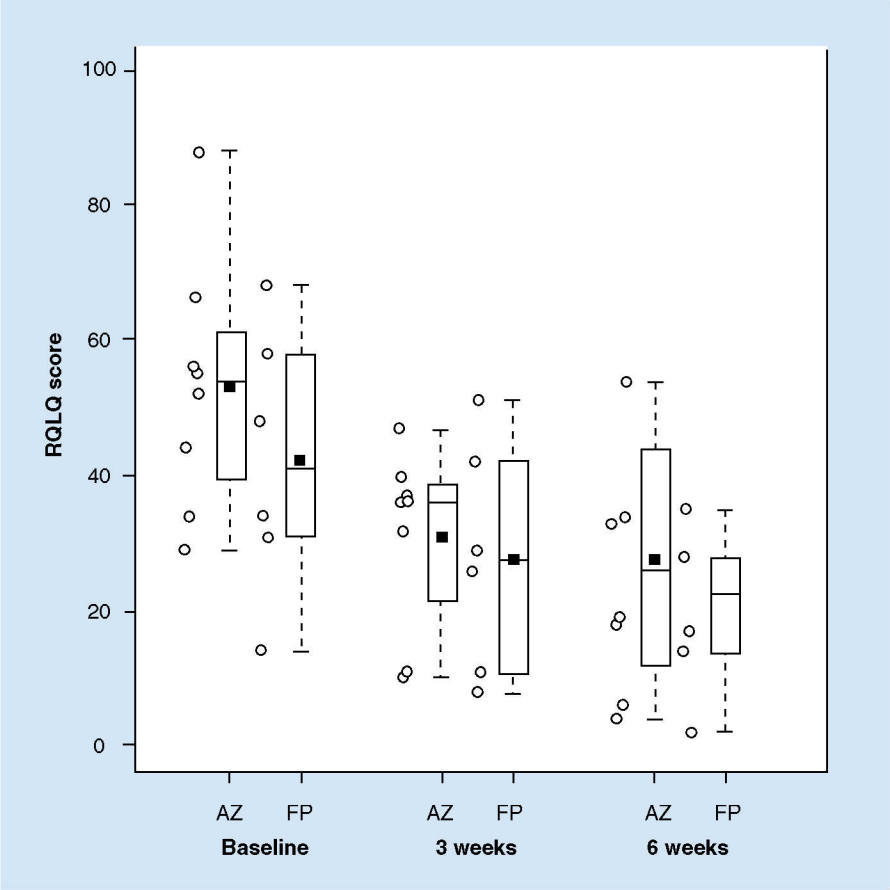

Figure 7. Effect of azelastine nasal spray or fluticasone propionate nasal spray on Rhinitis Quality of Life Questionnaire scores in geriatric patients with either allergic or nonallergic rhinitis.
AZ: Azelastine; FP: Fluticasone propionate; RQLQ: Rhinitis Quality of Life Questionnaire. Reprinted with permission from [29].

(≥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.