

Treatment with azelastine hydrochloride and fluticasone propionate in a single delivery device of young children and adolescents with allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) is the most common chronic noncommunicable disease worldwide that affects any age during the human life span but raises particular concerns among the parents and caregivers of the children who are affected. H₁-receptor antagonists and corticosteroids provide the most effective way of bringing the condition under control. Intranasal application of these medications has the advantage of a faster onset of action and avoids systemic unwanted adverse effects. The only combination treatment, which comprises azelastine hydrochloride and fluticasone propionate, so far in a single advanced delivery system has proven its efficacy and safety in clinical trials of adult patients with AR.

Objective: To critically review and identify gaps in the existing data for children in all different strata of pediatric ages.

Methods: We searched the specialized medical literature for publications on the efficacy and safety of the combined formulation of azelastine and fluticasone in a single delivery device in adolescents (ages < 18 years) and children (ages < 12 years).

Results: Altogether, 12 peer-reviewed articles have been published about trials that also involved subjects in different strata of the pediatric ages, seven of the articles pooled adolescents and adults. Three articles presented the results of studies in children ages 4 to 11 years specifically designed to overcome the difficulties that children experience in expressing themselves verbally.

Conclusion: All the trials with the novel combination product that involved young children and adolescents documented its efficacy, effectiveness, and safety. However, the numbers of the youngest children (ages 4 and 5 years) were low, which suggested that further data about safety and efficacy in this age group are needed.

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ALLERGIC RHINITIS WITH A FOCUS ON CHILDREN

Allergic rhinitis (AR) is defined as a symptomatic disorder induced by immunoglobulin E (IgE) mediated inflammation of the nasal structures after allergen exposure of individuals who are sensitized.¹ Its cardinal symptoms, identified in 1929, still compound the basis of its clinical diagnosis, and nowadays are supplemented by more sophisticated composite outcomes, such as disrupted daytime activities and night-time sleep, quality of life, impaired social behavior, psychological well-being, and cognitive functioning.^{2,3} The AR symptoms are nonspecific and are shared by other types of rhinitis related to different non-IgE-driven mechanisms, which renders the classification schemes intricate. The picture is getting even

more complex when also considering comorbidities as a measure of severity.⁴ The attitude toward AR has dramatically evolved over the past 2 decades, with the assumption that patients with rhinitis and asthma should be able to maintain a healthy and active life across their life span.⁵

AR is the most widespread chronic noncommunicable disease in all ages and walks of life. Its management is more-or-less standard during adulthood but poses specific requirements in childhood and in the elderly.^{6,7} A “runny” and “stuffy” nose in children is so common that parents often neglect it. However, symptoms of rhinitis can negatively impact the development of children because these symptoms affect learning ability and concentration.⁸ In addition, AR is often a forerunner of comorbidities such as asthma, sinusitis, nasal polyps. Associated frequent upper respiratory tract infections bring about adenoid hypertrophy, otitis media, eustachian tube dysfunction, and tympanic membrane retraction.^{9–11} All these circumstances reflect negatively on the mental state of children, and these children often experience psychological difficulties, anxiety, and depression.¹²

The most commonly used medications in pediatric practice, oral H₁-receptor antagonists, are generally

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well tolerated but still can, on rare occasions, suppress the tone of the central nervous system and cause a range of effects, from slight drowsiness to profound sleep.^{13,14} On rare occasions, paradoxical excitation may occur, particularly in infants and smaller children, which makes them irritable and hyperactive, with isolated cases of hallucinations and seizures.¹⁵ Therefore, choosing the most appropriate pharmaceutical product and application route in childhood and adolescence is a responsible task so as to avoid excessive sedation and activity impairment and other serious adverse events.^{16,17}

Pharmacologic treatment brings fast relief of the unpleasant symptoms of AR. The mainstays of treatment are the H₁-receptor antagonists and the nasally applied corticosteroids. Guidelines state that the management of the condition should rely on the type and severity of the separate symptoms as perceived by the patients, the properties of the available drug classes and the specific characteristics of the individual compounds within them, the preferences for specific products modeled by the media, and, last but not least, the modifying influence of financial considerations.^{17–20} However, in real life, very few patients are aware of the guidelines, and the usual practice is that they self-medicate by using over-the-counter medications in pharmacies.^{5,21}

Those patients who present to a physician's office in a primary care setting are usually prescribed medications, depending on their leading symptoms. Patients mostly fall into one of the two categories: "sneezers and runners" and "blockers."^{22,23} The leading symptoms of the "sneezers and runners" are rhinorrhea, itching, and sneezing. These symptoms are typically caused by histamine and, subsequently, are best neutralized by antihistamines. The lead congestion of the "blockers" requires the anti-inflammatory effect of corticosteroids. This division, however, is not absolute because there is overlap among the symptoms in the individual patients, which may also vary in the course of time. The response of patients to the seemingly "right drug" may be disappointing due to misleading posts on the internet or misinterpretation by the lay public.

Although adults, and to some extent adolescents, can make an informed choice based on their own perception of symptoms, the judgment about leading symptoms in children is made by their parents or guardians. Their assessment may be biased one way or another; to ensure coverage of all the symptoms, a combination of the two basic therapeutic approaches, antihistamines and nasal corticosteroids, would have a better chance of success in dependent children. Prescribing a single device for such a composite treatment is a prerequisite for increasing patients' compliance.

RATIONALE FOR THE INTRANASAL COMBINATION AZELASTINE HYDROCHLORIDE-FLUTICASONE PROPIONATE

Intranasal application of medications for AR treatment has certain advantages. Thus, the efficacy of intranasally applied antihistamines is higher than that of orally taken antihistamines.^{24,25} Another benefit is the faster onset (within 15 minutes) of the effect through the nasal route.²⁵ Azelastine nasal spray was demonstrated to produce significantly greater improvement in total nasal symptom scores and quality-of-life scores than did oral cetirizine.²⁶

As for intranasal corticosteroids, their topical application is highly effective and dramatically reduce the corticosteroid-associated risks related to their systemic use: the serum levels of newer formulations, such as fluticasone propionate and mometasone furoate, were below the detection threshold of the laboratory methods used for their detection, despite the high doses exceeding the maximum recommended doses for these formulations.²⁷ This is especially relevant for children, for whom concerns about corticosteroid-caused growth retardation, pituitary-adrenal axis suppression, immune system-associated complications, and a long list of other adverse effects are fueling fears of parents and guardians.²⁸

A number of patients with AR do not achieve optimal symptom control when treated with a single drug formulation. Two different compounds with complementary mechanisms of action could have a synergic effect when used in combination rather than separately. Thus, the primary antihistamine effect of azelastine, applied into the nose, could be enhanced by the anti-inflammatory activity of a topical corticosteroid-like fluticasone in subjects with persistent AR.²⁹

MAJOR CHARACTERISTICS OF THE COMPONENTS OF THE DRUG COMBINATION

The monopreparations azelastine and fluticasone had reached the pharmaceutical market some 30 years ago, with substantial amounts of clinical data about their clinical effectiveness and safety in both adults and children accumulated over the years.^{25,26}

Azelastine Hydrochloride

Azelastine is a phthalazine derivative that antagonizes the effect of histamine at H₁-receptors, also possessing properties of a mast cell stabilizer. It is prescribed in otorhinolaryngology as a nasal spray for AR and in ophthalmology as eye drops for allergic conjunctivitis.³⁰ It binds to the H₁-receptors on effector cells and prevents them from releasing histamine and other mediators, with ensuing early and late allergic responses. Studies that used human cell lines have documented inhibition by

azelastine of other mediators, such as leukotrienes and platelet-activating factor, as well as suppression of the accumulation and degradation of eosinophils at sites of allergic inflammation.³¹⁻³³

The systemic bioavailability of azelastine after nasal administration is ~40%.³⁴ Accordingly, its principal adverse effects are local (e.g., bitter taste, nasal burning, pharyngitis, paroxysmal sneezing), but adverse systemic effects (e.g., somnolence, headache) can also occur.³⁵ Anaphylactoid symptoms, breathlessness, chest pain, facial edema, diarrhea, involuntary muscle contractions, confusion, parosmia, paresthesia, pruritus, rash, urinary retention, vision abnormality, and xerophthalmia have occurred in patients who received azelastine nasal spray, but no definite causal relationship between these events and the drug have been established.

Fluticasone Propionate

Fluticasone is a high-potency synthetic trifluorinated glucocorticoid receptor agonist with topical anti-inflammatory properties and low systemic activity.³⁶ Applied intranasally, it is indicated to manage symptoms of both AR and non-AR, although experience is more extensive with AR.^{37,38} Fluticasone acts as a highly selective agonist at the glucocorticoid receptor, thereby producing anti-inflammatory and vasoconstrictive effects superior to a combination of cetirizine plus montelukast.³⁹ It has been shown to have a broad spectrum of inhibitory effects on several types of cells (eosinophils, mast cells, lymphocytes, macrophages, and neutrophils) and mediators (histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.⁴⁰

The propionate ester side chain renders fluticasone highly lipophilic, which facilitates its absorption and uptake across phospholipid cell membranes. Its systemic absorption, although, also accounting for any quantities swallowed in the gastrointestinal track, remains negligible.⁴¹ Common adverse events after nasal administration include stinging, burning, and bleeding in the nose; headache; nausea; vomiting and diarrhea; and very rarely, fever, sore throat, cough, facial swelling, hoarse voice, impaired swallowing, and difficult breathing.³⁷ A study in 250 children with moderate-to-severe AR documented the good tolerability of fluticasone nasal spray at doses 100 and 200 µg once a day (the latter being the usual adult dose); neither dosage seemed to interfere with the hypothalamic-pituitary-adrenal axis.⁴²

DEVELOPMENT OF THE COMBINATION PRODUCT

A forerunner of the azelastine-fluticasone combination therapy was a study conducted as early as 2008 by using the two components concurrently.⁴³ This was a

randomized, 2-week, multicenter, double-blind study performed in 151 subjects sensitized to Texas mountain cedar during the active pollen season.⁴³ They were allocated to three parallel groups: treatment with azelastine alone, fluticasone alone, and fluticasone applied 15 to 30 minutes after azelastine.⁴³ The three separate groups had statistically significant improvement of their baseline total nasal symptom score (TNSS) after 2 weeks of treatment; however, the improvement with the concurrent azelastine plus fluticasone treatment in terms of TNSS was significantly higher than the improvement with the individual products.⁴³

The combination of intranasal azelastine hydrochloride and fluticasone propionate in a single device (Dymista; Mylan Products Limited, Hertfordshire, United Kingdom), “is indicated for relief of symptoms of moderate-to-severe seasonal and perennial AR if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient.”⁴⁴ The licensed product azelastine-fluticasone (0.1%–0.0365%) is the first and, to our knowledge, the only preparation on the market and has proven to have advantage in the management of different rhinitis phenotypes. Its advanced nasal delivery system delivers with a single spray two different pharmaceutical compounds.

In an *in vitro* model of a human nasal cavity, the delivery of azelastine-fluticasone was retained in the targeted areas without spilling out of it.⁴⁵ In all the experiments, the combination product was observed to cover the turbinates but not drip into the nasopharynx.⁴⁵ Conversely, use of the original separate marketed intranasal monoproducts consecutively was associated with posterior or anterior runoff (which would mean diminished efficacy). The combination azelastine-fluticasone has been compared with either azelastine or fluticasone nasal sprays, and the synergistic effect of the combination has been well demonstrated; it afforded faster onset and better control of the AR symptoms in adult subjects with moderate and severe AR than in the separate components.⁴⁶⁻⁵²

INTRODUCTION OF AZELASTINE-FLUTICASONE IN THE PEDIATRIC PRACTICE

The clinical development and assessment of novel therapeutic preparations begin in patients at a mature age and is further expanded if relevant and needed to the extremes of the human life span. The safety and efficacy of the azelastine-fluticasone combination have been established in rigorous clinical trials, initially in adults and subsequently in children in line with the regulations of the European Medicines Agency.⁵³

In an effort to retrieve any relevant information on the use of azelastine and fluticasone in pediatric patients with AR, in October 2019, we performed a bibliographic search through PubMed of MEDLINE (the

Table 1 Studies on the combination Aze-Flu for intranasal use in the pediatric age in chronological order

Study, y	Pediatric Age, y	Design	Subjects, total no./no. on Aze-Flu*	Rhinitis Type	Study Duration
Hampel <i>et al.</i> , ⁶⁰ 2010	12–17	RDBPC, parallel group, efficacy and/or safety in adults and adolescents: Aze-Flu vs Aze vs Flu vs placebo#	610/153 (adolescents, not specified)	Seasonal	2 wk
Meltzer <i>et al.</i> , ⁶¹ 2013	12–17	RDBPC, parallel group, efficacy and/or safety in adults and adolescents: Aze-Flu vs Aze vs Flu vs placebo	779/193 (adolescents, not specified)	Seasonal	2 wk
Price <i>et al.</i> , ⁵⁹ 2013§	12–17	ROLAC, parallel group study, efficacy in adults and adolescents: Aze-Flu vs Flu	611/404 (adolescents, 36/28)	Perennial	1 y
Berger <i>et al.</i> , ⁵⁴ 2014§	12–17	ROLAC, parallel group study, safety in adults, and adolescents: Aze-Flu vs Flu	611/404 (adolescents, 36/28)	Allergic or nonallergic	1 y
Klimek <i>et al.</i> , ⁶² 2015	12–17	MCPNIS, adults and adolescents	1761/1761 (adolescents, 352/352)	Allergic	2 wk
Berger <i>et al.</i> , ⁵⁶ 2016	4–11	RDBPC, parallel groups, safety: Aze-Flu vs Aze vs Flu vs placebo	304/152 (ages 6–8 y, 119/59; 9–11 y, 185/93)	Seasonal	2 wk
Berger <i>et al.</i> , ⁵⁷ 2016¶	4–11	ROLAC, prospective, multicenter, parallel group, efficacy in children ages 6–11 y: Aze-Flu vs Flu	404/304 (ages 4–5 y, 51/40; 6–8 y, 172/128; and 9–11 y, 181/136)	Seasonal or perennial	3 mo
Scadding <i>et al.</i> , ⁵⁵ 2017	12–17	Multicenter, noninterventional study, retrospective data base analysis, adults and adolescents	193/193 (adolescents, 22/22)	Allergic, non-allergic, unknown	1 y
Agache <i>et al.</i> , ⁶³ 2018	12–17	MCPNIS, adults and adolescents	253/253 (adolescents, 13/13)	Allergic	2 wk
Berger <i>et al.</i> , ⁵⁸ 2018¶	4–11	ROLAC, prospective, multicenter, parallel-group, safety in children ages 6–11y: Aze-Flu vs Flu	404/304 (ages 4–5 y, 51/40; 6–8 y, 172/128; and 9–11 y, 181/136)	Seasonal or perennial	3 mo
Haahr <i>et al.</i> , ⁶⁴ 2019	12–17	MCPNIS, adults and adolescents	170/170 (adolescents, 7/7)	Allergic, non-allergic, unknown	2 wk
Stjarne <i>et al.</i> , ⁶⁵ 2019	12–17	MCPNIS, adults and adolescents	431/431 (adolescents, 18/18)	Allergic, non-allergic, unknown	2 wk

Aze = Azelastine hydrochloride; Flu = fluticasone propionate; RDBPC = randomized, double-blind, placebo controlled; ROLAC = randomized, open label, active controlled; MCPNIS = multicenter, prospective, noninterventional study.

*Data in parentheses are age group, total no. subjects in age group/no. subjects in age group on Aze-Flu [in bold].

#Aze and Flu were not in a single device but were applied consecutively.

§Published on the same study population.

¶Published on the same study population.

database of the National Center for Biotechnology Information, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda MD, USA) by using as search terms with Boolean operators: “azelastine” AND “fluticasone” AND “allergic rhinitis” AND “children” OR “adolescents” OR “pediatric age”. Twelve publications that presented original work that involved subjects in pediatric age were retrieved (Table 1).

Nine of these studies^{54,55,59–60} present work done in six trials that recruited adolescents, along with adults and three publications^{56–58} on two trials in children aged between 4 and 11 years. The adolescent subjects had been recruited and analyzed on equal footing with the adults, and only two publications derived from one trial explicitly indicate their number.^{54,55} The children in the dedicated three studies for ages < 12 years had been stratified into age intervals 4–5, 6–8, and 9–11 years, with few numbers of included subjects in the lowest age stratum.^{56–58} A total of 3212 subjects had been exposed to azelastine-fluticasone intranasal single-delivery device combination, of whom, an unknown number had been adolescents, and 456 children had been between 4 and 11 years of age: 40 of them between 4 and 5 years, 187 between 6 and 8 years, and 229 between 9 and 11 years (Fig. 1, a–c).

The studies that involved subjects in the pediatric ages had basically followed the “randomized, double-blind, actively controlled, or placebo controlled, parallel group” type design, comparing the combination product to one^{54,56,57,59} or both components with or without placebo.^{43,56,60,61} The efficacy studies used reflective TNSS, change from baseline as primary outcome. Secondary outcomes also included individual symptom scores, ocular symptoms, symptom-free days, and time to achieve a symptom-free day,⁵⁹ quality of life assessed by a (Pediatric) Rhinoconjunctivitis Quality of Life Questionnaire.^{52,53,56}

Collection of safety information was part of all study protocols, but two trials were particularly focused on safety issues.^{54,58} The overall incidence of treatment-related adverse events in adults and adolescents was low, with both the azelastine-fluticasone combination product (9.4%) and its comparator fluticasone (11.1%), without evidence of early or late adverse events.⁵⁴ In the same study, nasal examinations showed no evidence of nasal mucosal ulcerations or septal perforations with the combination product, and, on the whole, the incidence of unwanted events had been reduced as the study progressed.⁵⁴ No unusual or unexpected signs had been observed on examination of the eyes; no clinically significant deviations were found within the laboratory results.⁵⁴ The comparison among the fasting serum cortisol levels after 12 months of treatment did not uncover clinically significant differences among the groups.⁵⁴

In the other study of children in the age range between 4 and 11 years, the incidence of adverse

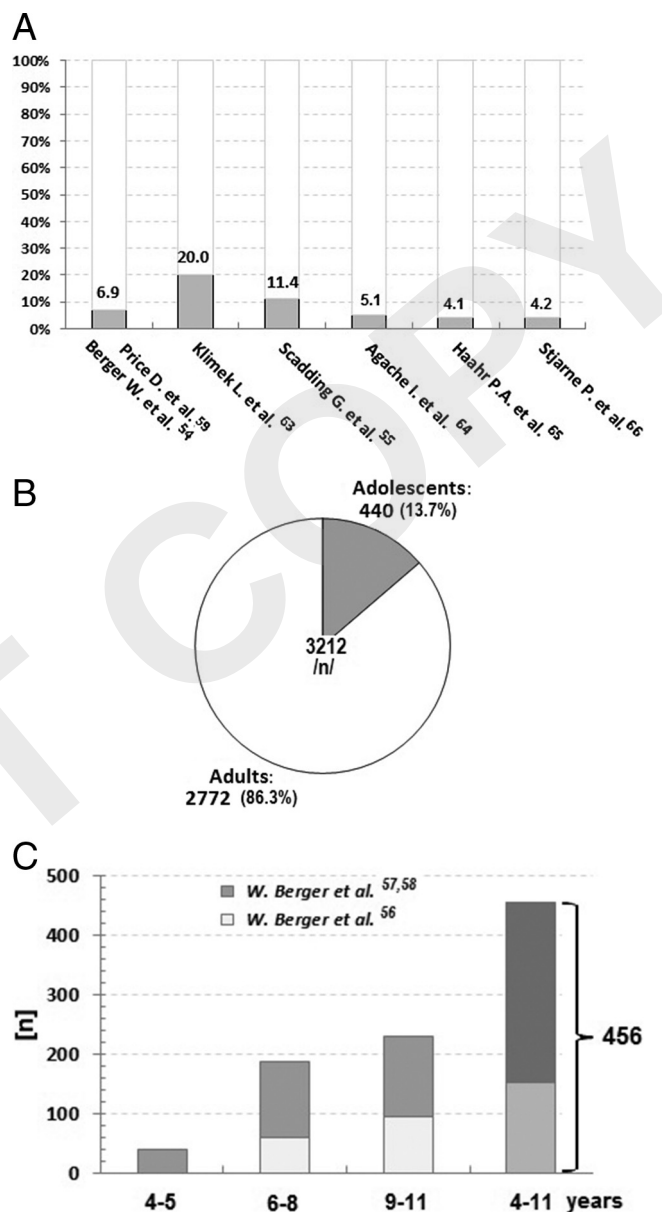


Figure 1. Graphic summary of the numbers of subjects from different strata of the pediatric age included in trials with the azelastine-fluticasone (AzeFlu) combination product. (a) Proportion of adolescent subjects in trials of subjects ages > 12 years; (b) absolute and relative numbers of adolescent patients in the studies of subjects ages > 12 years; and (c) stacked bar graphs, summing up the numbers of the children ages 4–5, 6–8, and 9–11 years in the two trials dedicated to the ages < 12 years.

events presumably related to treatment was not found to be different between the combination product (16%) and the fluticasone (12%) groups after 90 days of continuous use.⁵⁸ The most frequent of these events in both groups was epistaxis (9% versus 9%, respectively), followed by headache (3% in the combination product group versus 1% in the fluticasone group). All

other adverse events were registered in <1% of the cases, the majority of them being of mild intensity and of resolving spontaneously. In both groups, nasal examinations showed gradual improvement in the course of time, with no cases of septal perforation or mucosal ulceration. Similarly, no unexpected changes or unusual findings in laboratory parameters or vital signs emerged.

Three of the studies had been planned and carried out as non-interventional.^{55,62,65} The intent of one study in the United Kingdom was to characterize the type of patients to whom the azelastine-fluticasone combination was prescribed in real-life setting.⁵⁵ The profile of this population suggested that these were individuals ages > 12 years with moderate-to-severe AR, irrespective of the type of previous monotherapy or multiple AR treatments, with numerous preceding physician visits for AR with therapeutic failures, unable to cope with anticipated allergen exposure and constantly needing relief of bothersome symptoms.⁵⁵

A multicenter study in Germany was performed to assess the use and effectiveness of the azelastine-fluticasone combination in routine clinical practice.⁶² It included 1781 patients with AR and overt symptoms assessed to be >50 mm on a visual analog scale.⁶² After being assigned to the intranasal combination, they were reassessed at days 1, 3, 7, and after ~14 days.⁶² Every second patient felt symptom improvement and good control by day 3, and there were no significant differences among the adolescents, the adults, and the older adults.⁶² The type of AR, seasonal, perennial, or mixed, and the severity of the disease did not seem to make a difference; all the subjects perceived effective and rapid symptom control.⁶² Responder rates in this real-life study were higher than those in the conventional controlled clinical trials.

Real-life multicenter studies similar to the German study⁶² using visual analog scales to assess the therapeutic effect of the combined azelastine-fluticasone nasal spray were conducted in Romania, Denmark, and Sweden.^{63–65} The recruited subjects involved adolescents ages >11 years, along with adult patients with moderate-to-severe AR.^{63–65} The assessments were made within a period of ~2 weeks after initiation of treatment, and the effectiveness of the formulation did not depend on the disease severity, phenotype of AR, or the age of the subjects, equally providing rapid and sustained symptoms control. These studies did not differentiate between adolescents and adults.

PECULIARITIES OF OUTCOMES ASSESSMENT IN CLINICAL TRIALS IN YOUNGER CHILDREN

Using subjective measures when conducting clinical trials in children with AR is associated with certain

constraints, which are inversely proportional to the age of the child. Efficacy and safety evaluations such as reflective TNSS and quality-of-life scores in these studies are confounded by the subjective judgment of the parents or guardians or caregivers. The reporting of efficacy outcomes and adverse events by the children may be limited by their inability to express themselves properly and by the interpretation of the caregivers, who may not be able to grasp the essence of what the child is experiencing. The symptoms assessment by children and caregivers cannot be assumed to be the same; using pediatric-generated data would be preferable whenever possible. Despite this “white noise,” the signals of both efficacy and safety could be captured in the trials of the azelastine-fluticasone combination, and the outcomes did not differ dramatically from those of adolescents and adults.^{56–58}

FUTURE PERSPECTIVES

As opposed to asthma inhalatory treatment, in which a long list of double and, lately, triple combinations of compounds in a single inhaler have gained access to the pharmaceutical market, there is just one combination of an antihistamine plus corticosteroid for nasal application, which has become available recently for AR management. Time will tell if the benefits of this approach will achieve wide recognition, which, in turn, would stimulate the development of other compounds in a single delivery system. Cost-effectiveness issues may also come into consideration when taking strategic decisions by the pharmaceutical industries. As for the application of the so-far only one marketed combination product of nasal antihistamine and corticosteroid in a single delivery device in the pediatric age, our overview suggested that there is a relative paucity of data from dedicated studies in adolescents and especially in younger children to cover all different aspects of its use.

CONCLUSION

The relatively few trials on the use of the combination azelastine-fluticasone in a single device for nasal application in childhood are positive both in terms of efficacy and safety for the ages between 4 and 17 years. The sparse data for the youngest children (ages 4–5 years), though, would require collection of more real-life information for that age group.

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