ORIGINAL ARTICLE

Efficacy and Safety of Desloratadine/ Pseudoephedrine Combination vs Its Components in Seasonal Allergic Rhinitis

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Abstract

Background: Antihistamines are first-line therapy for the treatment of seasonal allergic rhinitis (AR); however, an oral decongestant is often added to improve control of nasal congestion.
Objective: To examine whether a tablet combining the nonsedating antihistamine desloratadine and the decongestant pseudoephedrine was more effective than either drug administered alone in reducing the symptoms of seasonal AR, including nasal congestion.
Patients and Methods: In this multicenter, double-blind study, participants (N = 598) with symptomatic seasonal AR were administered either a combination tablet of desloratadine 2.5 mg/pseudoephedrine 120 mg (DL/PSE) bid, a desloratadine 5.0 mg qd and a placebo tablet, or pseudoephedrine 120 mg bid. Participants assessed their symptom severity twice daily over the 2-week treatment period.
Results: The primary variable to assess the effects of the antihistamine component—mean change from baseline in average AM/PM reflective total symptom score (TSS), excluding nasal congestion—was significantly greater (–6.54) for DL/PSE than for desloratadine (–5.09) or pseudoephedrine (–5.07) monotherapy ($P < .001$ for both). The primary variable to assess the effects of the decongestant component—mean change from baseline in average AM/PM reflective nasal congestion score—was also significantly greater (–0.93) for DL/PSE than for desloratadine (–0.66) or pseudoephedrine (–0.75) ($P < .001$ vs desloratadine; $P = .006$ vs pseudoephedrine).
Conclusion: This study demonstrated that DL/PSE therapy was more effective in reducing symptoms of seasonal AR, including nasal congestion, than the individual components when administered alone, thus supporting use of this combination in participants with symptomatic seasonal AR and prominent nasal congestion.

Key words: Allergic rhinitis. Antihistamine. Congestion. Desloratadine. Pseudoephedrine.

Resumen

Antecedentes: los antihistamínicos son la primera línea terapéutica en el tratamiento de la rinitis alérgica (RA) estacional; sin embargo, se añade a menudo un descongestionante oral para mejorar el control de la congestión nasal.
Objetivo: Examinar si un comprimido que combina el antihistamínico no sedante desloratadina y el descongestionante pseudoefrina es más eficaz que los dos fármacos administrados aisladamente, en la reducción de los síntomas de la RA estacional, incluyendo la congestión nasal.
Pacientes y Métodos: En este estudio multicéntrico, doble ciego, a los participantes (N = 598) con RA estacional sintomática se les administró la combinación de desloratadina 2,5 mg/pseudoefedrina 120 mg (DL/PSE) dos veces al día, desloratadina 5,0 mg una vez al día y un comprimido de placebo, o pseudoefedrina 120 mg dos veces al día. Los participantes evaluaban sus síntomas 2 veces al día diariamente durante las 2 semanas de tratamiento.
Resultados: La variable primordial para evaluar los efectos del componente antihistamínico –analizando el cambio medio con respecto al momento basal la puntuación total de síntomas (PTS) mañana/tarde, y excluyendo la congestión nasal– fue significativamente mayor (–6,54) para DL/PSE comparada con desloratadina (–5,09) o pseudoefedrina (–5,07) en monoterapia ($P < 0,001$ for both). La principal variable para evaluar los efectos del componente descongestionante –el cambio medio con respecto al momento basal, la puntuación de la congestión nasal mañana/tarde– fue también significativamente mayor (–0,93) para DL/PSE que para la desloratadina (–0,66) o pseudoefedrina (–0,75) ($P < 0,001$ vs desloratadina; $P = 0,006$ vs pseudoefedrina).
Conclusión: Este estudio demostró que la terapia DL/PSE fue más eficaz en la reducción de síntomas de la RA estacional, incluyendo la congestión nasal, que cuando se administran los componentes individualmente, apoyando de esta forma el uso de esta combinación en pacientes con RA estacional sintomática y gran congestión nasal.

Palabras clave: Rinitis alérgica. Antihistamínico. Congestión. Desloratadina. Pseudoefedrina.

Introduction

Allergic rhinitis (AR) is among the world's most common chronic diseases [1]. Over the past several decades, the global prevalence of AR has increased [2,3], with the result that it now affects approximately 24% of the population in many European countries [4-7]. Epidemiologic studies estimate the percentage of undiagnosed participants at 24%-45% [4,8], suggesting that an even greater proportion of the population may be affected. The estimated annual costs attributable to AR are as high as $9.7 billion [9].

The main symptoms of AR include nasal congestion, rhinorrhea, itching, sneezing, and nonnasal symptoms, such as burning, itching, and watery eyes or itching ears and palate. These symptoms can interfere with cognitive and emotional functioning and have been shown to exact a considerable toll on patients' quality of life [10-12]. In a survey of 5 European countries (France, Germany, Italy, Spain, and the United Kingdom), 84.2% of patients with AR reported that their symptoms had a deleterious effect on daily activities [10]. Nasal congestion in particular—which patients consider to be the most bothersome symptom of AR—is associated with sleep disturbances that can result in impaired work productivity, learning, and concentration [13-16]. In the 5-country survey, nasal congestion was reported as currently or frequently present by 84% of patients with AR [10].

Histamine is thought to be the key mediator responsible for many of the symptoms of AR [17]. Histamine$_1$-receptor (H_1-receptor) antagonists can be effective at relieving AR symptoms, such as sneezing and rhinorrhea, and oral nonsedating antihistamines are therefore recommended as first-line therapy for the disease [18]. Some of these medications are moderately effective at treating congestion [19], possibly because nasal stuffiness is also caused by vasoactive mediators other than histamine [20]. Consequently, treatment guidelines recommend antihistamines in combination with a decongestant in selected patients to control the full spectrum of AR symptoms [18,21].

Desloratadine, a nonsedating second-generation antihistamine that is highly selective for the H_1-receptor, has demonstrated efficacy in the treatment of AR [10,22-29]. A recent meta-analysis of clinical trials for AR found that participants treated with desloratadine had significantly fewer nasal eosinophils and significantly higher nasal airflow than those receiving placebo [10,30]. As a result, some authors have suggested that desloratadine may possess decongestant activity [12,29,31] that is not mediated through the H_1-receptor [32], which may be related to inhibition of the expression of histamine-induced cytokines and proinflammatory mediators [27]. Although the beneficial effects of desloratadine on nasal congestion and airflow have been demonstrated in a number of clinical studies [22-24,29-31], they are moderate in magnitude, and some patients with prominent nasal congestion may require adjunctive therapy with a nasal decongestant.

Pseudoephedrine, a sympathomimetic nasal decongestant, demonstrates variable efficacy against histamine-mediated symptoms of AR when used as monotherapy [33]. Clinical studies have shown that combining pseudoephedrine with an antihistamine produces an added benefit in that it alleviates many of the symptoms of AR, particularly nasal congestion [34,35].

Desloratadine 2.5 mg/pseudoephedrine 120 mg (DL/PSE) is a bilayer combination tablet consisting of immediate-release desloratadine 2.5 mg and sustained-release pseudoephedrine sulfate 120 mg designed for twice-daily dosing. The present study was undertaken to evaluate whether this combination would reduce symptoms of seasonal AR, including nasal congestion, more effectively than either component alone. The study also evaluated the safety profile of DL/PSE according to participant-reported adverse events (AEs), electrocardiograms, vital-sign evaluations, and laboratory test results.

Methods

Study Design

This multicenter study conducted during the fall allergy season employed a randomized, double-blind, parallel-group design. After a 3- to 14-day run-in period, eligible participants were randomized at baseline (Day 1) to receive DL/PSE bid, desloratadine 5 mg qd and a placebo tablet, or pseudoephedrine 120 mg bid for 15 consecutive days using a double-dummy technique to preserve blinding. The assigned study drug was administered orally in the morning (2 tablets) and the evening (1 tablet), without regard to the timing of meals or other daily activities. Participants were followed up at Days 8 (Visit 3) and 15 (Visit 4). Pollen counts were recorded throughout the study period.

Study Population

The study was designed to recruit about 30 participants at each of approximately 20 medical centers across the United States to ensure participation by 600 evaluable participants. Those aged ≥12 years, of either sex and of any race, with a ≥2-year documented history of seasonal AR, were eligible to participate in the study. Sensitivity to a seasonal allergen was confirmed with a positive skin prick test result or an intradermal test response to an appropriate seasonal allergen.

Participants were required to be free of any clinically significant disease other than seasonal AR that would interfere with the study evaluation, including hematopoietic, cardiovascular, hepatic, renal, neurologic, psychiatric, or autoimmune diseases. Other exclusion criteria included asthma requiring long-term use of inhaled or systemic corticosteroids, clinically significant sinusitis or chronic purulent postnasal drip, rhinitis medicamentosa, upper respiratory tract or sinus infection, nasal structural abnormalities, and pregnancy or lactation.

Participants who had used any drug in an investigational protocol in the 30 days prior to screening were excluded, as were those who were dependent on decongestants (nasal, oral, or ocular), nasal topical antihistamines, or nasal corticosteroids. Participants receiving immunotherapy were also excluded unless they were on a regular maintenance schedule prior to screening. These participants were required not to receive immunotherapy within 24 hours before a follow-up visit.

Efficacy Evaluations

Participants recorded the severity of their seasonal AR symptoms on diary cards using a 4-point scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe). Signs and symptoms of seasonal AR evaluated were both nasal (congestion, rhinorrhea, itching, sneezing) and nonnasal (itching or burning eyes, tearing or watering eyes, reddened eyes, and itching ears or palate). Participants completed symptom assessments twice daily (AM and PM approximately 12 hours apart), recording both how they felt over the previous 12 hours (reflective) and at the time of assessment (instantaneous).

Participants qualified for enrollment at the initial screening visit if their reflective sign/symptom scores (as assessed by both participant and investigator) were as follows: congestion ≥ 2, rhinorrhea ≥ 2, total nasal symptom score (TNSS) ≥ 6, and total nonnasal symptom score (TNNSS) ≥ 5. Participants qualified for randomization at the baseline visit if their scores for the previous 3 days and the morning of the baseline visit were as follows: total rhinorrhea ≥ 14, total congestion ≥ 14, TNSS ≥ 42, and TNNSS ≥ 35. Participants continued to record reflective and instantaneous AM and PM symptom severity scores twice daily throughout the study.

Efficacy Endpoints

The primary efficacy variable for the antihistamine component of DL/PSE was the mean change from baseline in average AM/PM reflective total symptom score (TSS) (excluding nasal congestion) compared with pseudoephedrine monotherapy over the 15-day treatment period. The primary efficacy variable for the decongestant component of DL/PSE was the mean change from baseline in average AM/PM reflective nasal congestion score compared with desloratadine monotherapy over the 15-day treatment period. Secondary efficacy variables included TSS, TNSS, TNNSS, individual symptom scores, overall condition of seasonal AR, and response to therapy.

Safety Evaluations

Vital signs were measured at each visit. Twelve-lead electrocardiograms, complete blood cell counts, serum blood chemistry profiles, and complete urinalyses were performed at the screening visit and at the final visit. Adverse events were evaluated by diaries and through participant interviews.

Statistical Analysis

Primary efficacy variables were analyzed using a 2-way analysis of variance (ANOVA) model, which could identify sources of variation due to both treatment and center. For the primary statistical comparison of the change from baseline in the mean AM/PM reflective TSS (excluding nasal congestion) with DL/PSE versus desloratadine and pseudoephedrine monotherapy, a sample size of 200 evaluable participants per treatment group, a 2-tailed α-level of .05, and a pooled standard deviation of 4.25 points on the change from baseline was required to detect differences of ≥ 1.6 points between treatment groups with a power of ≥ 90%. For the primary statistical comparison of the change from baseline in the average AM/PM reflective nasal congestion score with DL/PSE versus desloratadine and pseudoephedrine, a similar sample size of 200 evaluable participants per treatment group, a 2-tailed α-level of .05, and a pooled standard deviation of 0.6 points on the change from baseline were required to detect differences of ≥ 0.2 between treatment groups with a power of ≥ 90%. With 200 participants in each treatment group, the overall power for both comparisons being statistically significant was ≥ 88%.

Results

Of the 598 participants receiving at least 1 dose of a study medication, 561 (93.8%) participants completed the study: 189 were treated with DL/PSE, 191 with desloratadine

Table. Baseline Demographic and Clinical Characteristics

Characteristic	Desloratadine/ pseudoephedrine (2.5/120 mg bid)	Desloratadine (5 mg qd)	Pseudoephedrine (120 mg bid)
Patients, No.	200	198	200
Mean age (range), y	34.9 (12-74)	37 (12-76)	35 (12-68)
Men/women	79/121	69/129	76/124
Race, No. (%)			
Caucasian	161 (81)	152 (77)	163 (82)
Black	24 (12)	26 (13)	19 (10)
Asian	4 (2)	4 (2)	6 (3)
Hispanic	8 (4)	13 (7)	7 (4)
American Indian	0	0	1 (1)
Other	3 (2)	3 (2)	4 (2)
Mean duration of seasonal AR (range), y	19.6 (2-69)	17.9 (2-56)	18.0 (2-54)
Mean baseline scores:			
AM/PM reflective TSS score (excluding nasal congestion)	14.18	14.82	14.06
AM instantaneous TSS score (excluding nasal congestion)	13.87	14.75	13.82
AM/PM reflective nasal congestion score	2.47	2.50	2.46
AM instantaneous nasal congestion score	2.42	2.50	2.45

Abbreviations: AR, allergic rhinitis; TSS, total symptoms score.

monotherapy, and 181 with pseudoephedrine monotherapy. Demographic and baseline characteristics were similar across the 3 treatment groups (Table 1).

Efficacy

The primary efficacy variable to assess the effects of the antihistamine component was mean change from baseline in average AM/PM reflective TSS, excluding nasal congestion. The primary efficacy variable for the decongestant component was mean change from baseline in average AM/PM reflective nasal congestion score.

During the 15-day treatment period, DL/PSE was significantly more effective than either desloratadine or pseudoephedrine monotherapy at reducing the TSS, excluding nasal congestion ($P<.001$ for both comparisons). At the end of the study, DL/PSE reduced AM/PM reflective TSS by –6.54 (–46.0%), compared with –5.09 (–33.5%) for desloratadine and –5.07 (–35.9%) for pseudoephedrine (Figure 1). The DL/PSE combination was also significantly more effective than either component alone at reducing nasal congestion ($P<.001$). Mean reductions from baseline in AM/PM reflective nasal congestion scores were –0.93 (–37.4%) for DL/PSE compared with –0.66 (–26.7%; $P<.001$) for desloratadine and –0.75 (–31.2%; $P=.006$) for pseudoephedrine (Figure 2).

Significant improvement in nasal congestion was observed as early as Day 2 and at all subsequent time points in participants treated with DL/PSE compared with those treated with desloratadine monotherapy ($P< .005$). Treatment with DL/PSE also produced significantly greater reductions in the mean AM instantaneous nasal congestion score –0.81, –33.0%) than desloratadine (–0.60, –22.8%) ($P=.002$) and pseudoephedrine (–0.66, –27.7%) ($P=.032$). Over the course of the study, DL/PSE was also associated with a significantly greater improvement in AM/PM instantaneous TSS (excluding nasal congestion) than desloratadine and pseudoephedrine monotherapy, with mean reductions from baseline of –6.27 (–45.1%) versus –4.92 (–35.6%; $P<.001$) and –5.19 (–35.2%; $P=.011$), respectively.

The mean changes from baseline in AM and PM reflective and instantaneous TSS (excluding nasal congestion) over the 15-day treatment period are presented in Figure 3. In general, results from the participant-evaluated reflective 12-hour and instantaneous time periods were similar to those observed for the primary reflective AM/PM time period. Mean reductions from baseline of –1.06 (–40%), –0.95 (–33.8%), and –0.91 (–33.6%) were observed in the overall condition of seasonal AR with DL/PSE, desloratadine, and pseudoephedrine, respectively, but only the improvement with DL/PSE versus pseudoephedrine approached statistical significance ($P=.062$).

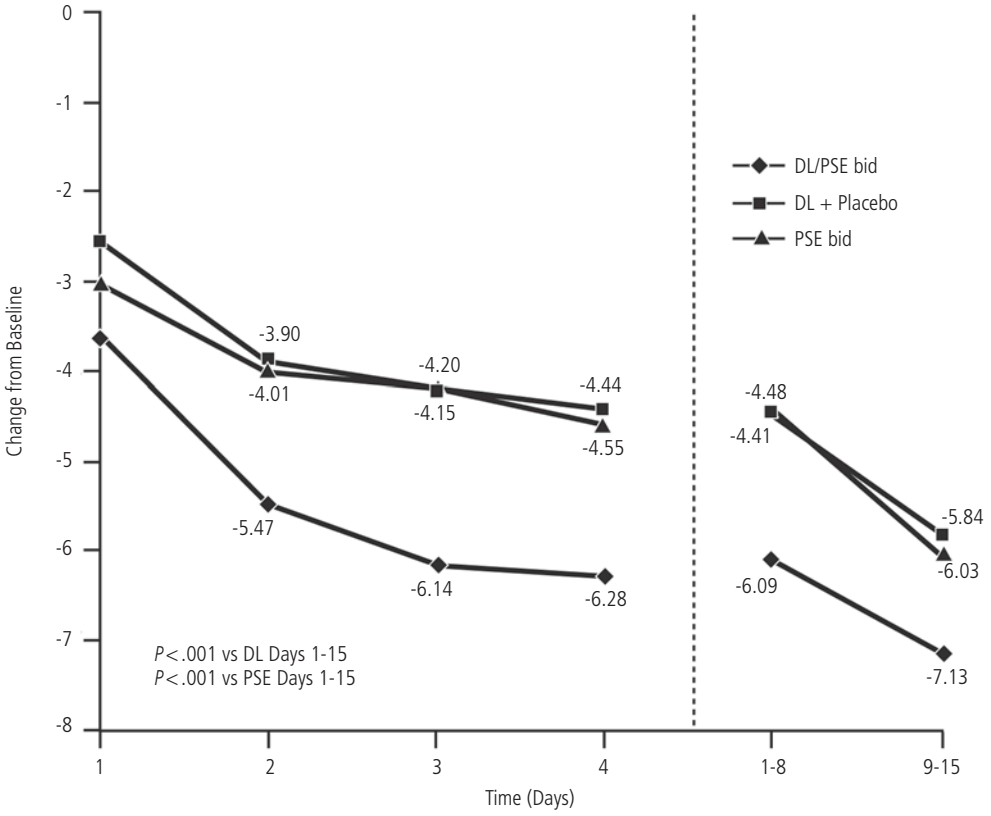

Figure 1. AM/PM reflective total symptom score (excluding nasal congestion). bid indicates twice a day; DL, desloratadine; PSE, pseudoephedrine.

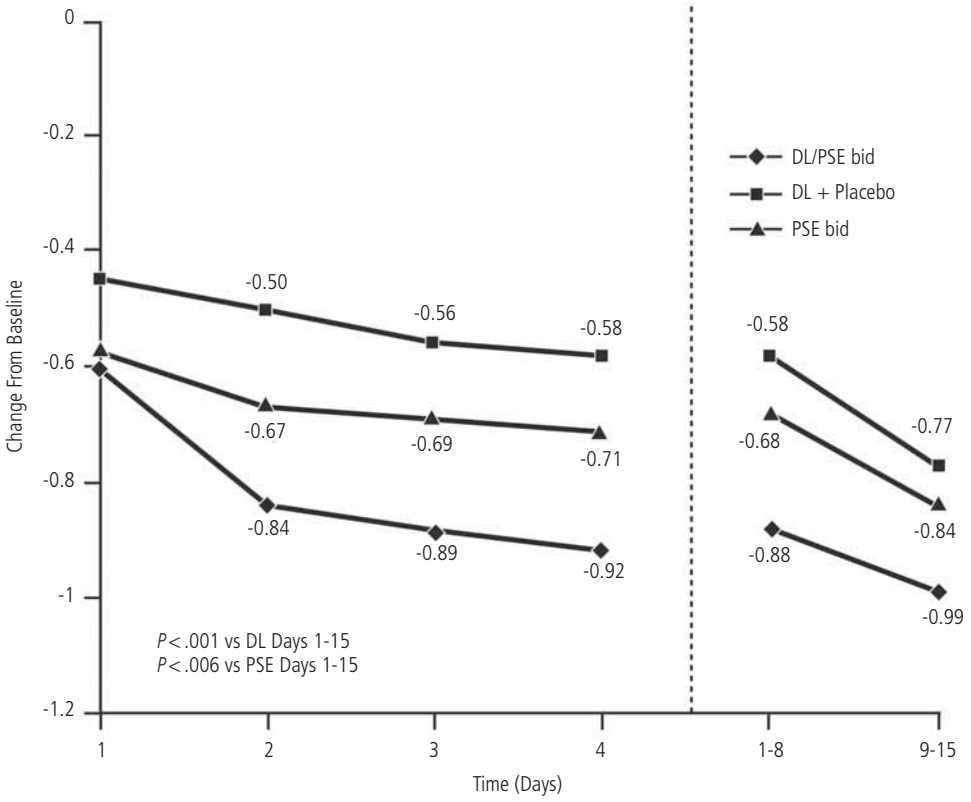

Figure 2. AM/PM reflective nasal congestion score. bid indicates twice a day; DL, desloratadine; PSE, pseudoephedrine.

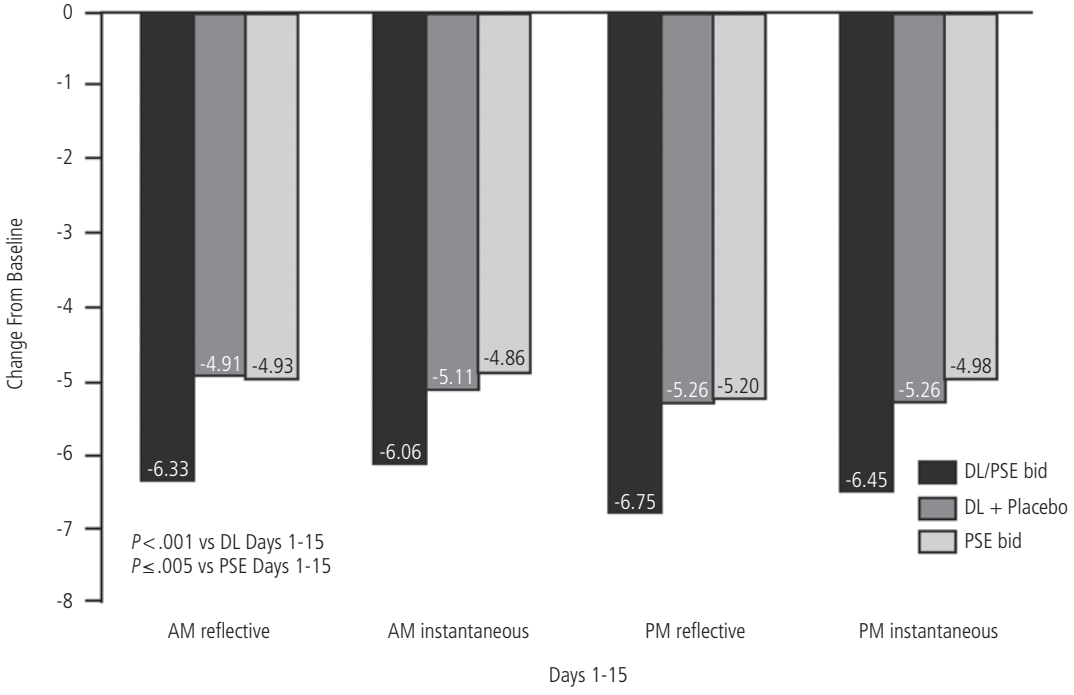

Figure 3. Other total symptom scores (excluding nasal congestion). bid indicates twice a day; DL, desloratadine; PSE, pseudoephedrine.

Safety

The DL/PSE formulation was safe and well tolerated, and no serious or unexpected AEs were reported. The most frequently reported AEs among participants who received DL/PSE were dry mouth (9.5%), insomnia (9.5%), and headache (6.5%), which were similar to the corresponding frequencies in the pseudoephedrine monotherapy group (8.0%, 14.0%, and 12.0%, respectively). The rates of dry mouth, insomnia, and headache in the desloratadine monotherapy group were lower: 2.0%, 3.0%, and 7.1%, respectively.

Of the 20 participants who discontinued the study due to AEs, 7 (3.5%), 9 (4.5%), and 4 (2.0%) were in the DL/PSE, pseudoephedrine, and desloratadine groups, respectively. Small increases in mean heart rate were observed among participants in the DL/PSE and pseudoephedrine groups (3.9 and 3.0 bpm, respectively). No clinically relevant changes in median values for laboratory parameters, mean vital sign values, or electrocardiogram intervals (including corrected QT intervals) were observed.

Discussion

This study was undertaken to investigate the effects of a combination tablet of desloratadine 2.5 mg and pseudoephedrine 120 mg, administered twice daily, in participants with seasonal AR. The antihistaminic efficacy of DL/PSE was significantly greater ($P < .001$) than that of pseudoephedrine monotherapy throughout the study. The DL/PSE formulation was also significantly more effective than desloratadine alone in reducing nasal congestion ($P < .001$). Similar results were observed for other composite and individual symptom scores. Overall, these results show that combining desloratadine and pseudoephedrine in a single formulation resulted in an additional antihistaminic and decongestant effect. The formulation was safe and well tolerated, with AEs in the DL/PSE group being similar to those reported in the pseudoephedrine monotherapy group.

The results presented here support those of previous studies that examined the benefits of combination therapy with a second-generation antihistamine and a decongestant, including desloratadine [34-38]. While desloratadine monotherapy has demonstrated decongestant activity in randomized, placebo-controlled trials [10,39], findings in the present study support an additional beneficial effect, especially on congestion, of DL/PSE.

Nasal congestion is common in patients with AR. In one European survey, most respondents reported having nasal congestion: France (54%), Germany (60%), Italy (50%), Spain (49%), and the United Kingdom (63%) [40]. Similarly, a US-based survey found that 85% of patients with AR had nasal congestion, and 76% of them described it as moderate or severe [41]. Adults (48%) and children (58%) indicated that nasal congestion was the most bothersome symptom of their AR.

Allergic rhinitis, especially the symptom of nasal congestion, impairs quality of life, interferes with cognitive and emotional functioning, and reduces work/school productivity, all of which exert a substantive burden on society [13-16]. Between 70% and 86% of respondents in the above-mentioned European survey rated nasal congestion as disruptive or extremely disruptive to sleep: France 86%, Germany 74%, Italy 70%, and the United Kingdom 73% [40]. More than 80% of respondents to the US survey reported that nasal congestion made it difficult to fall asleep or caused them to wake up [41]. Sleep impairment due to nasal congestion leads to the daytime fatigue frequently reported by patients with AR [40,42,43].

In the US survey, individuals with AR reported that nasal congestion was the symptom they most wanted to prevent and for which they were more likely to seek treatment (54% of adults and 69% of children) [41]. Respondents placed the greatest value on medications that provide effective, long-lasting relief of congestion. While 75% of those receiving medication for nasal congestion were satisfied with their treatment, only 13% reported being very satisfied. DL/PSE was associated with a rapid and sustainable improvement in congestion from baseline—even more than that of desloratadine monotherapy—suggesting that this combination represents a valuable treatment option for patients who do not achieve sufficient control of nasal congestion with desloratadine alone. Patient satisfaction with medication correlates with improved adherence to treatment regimens, and clinical studies demonstrate that adherence to treatment is a determining factor in better health outcomes [44].

The data in this study demonstrated that the combination of desloratadine 2.5 mg and pseudoephedrine 120 mg bid was well tolerated and provided effective relief from the symptoms of seasonal AR, including nasal congestion, rhinorrhea, itching, sneezing, itching/burning eyes, and tearing/watering eyes. The combination formulation was significantly more effective in treating these nasal and nonnasal symptoms than either component alone, thus substantiating the value of DL/PSE in the treatment of patients with seasonal AR, especially those for whom nasal congestion is a prominent symptom.

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