

Intranasal Azelastine and Fluticasone as Combination Therapy for Allergic Rhinitis: Systematic Review and Meta-Analysis

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Otolaryngology–
Head and Neck Surgery
1–7
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DOI: 10.1177/0194599819841883
http://otojournal.org


Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Received November 27, 2018; revised January 4, 2019; accepted March 14, 2019.

Abstract

Objective. Combination therapy with intranasal azelastine and fluticasone propionate is an option for treatment of allergic rhinitis. This systematic review and meta-analysis examines existing literature to determine efficacy in treating allergic rhinitis compared to monotherapy.

Data Sources. The PubMed, EMBASE, Cochrane, and MEDLINE databases were systematically searched for randomized controlled trials using AzeFlu nasal spray.

Review Methods. Randomized, controlled trials that reported symptom relief of allergic rhinitis in males and females of all ages were included. Results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard.

Results. Systematic review identified 8 articles suitable for review. The risk of bias was generally low. All studies exhibited a greater decrease in patient-reported symptom scores in patients treated with combination therapy compared to monotherapy or placebo. Meta-analysis revealed superiority of combination therapy in reducing Total Nasal Symptom Score compared to placebo (mean change from baseline: -2.41 ; 95% confidence interval [CI], -2.82 to -1.99 ; $P < .001$; $I^2 = 60\%$), azelastine (mean change from baseline: -1.40 ; 95% CI, -1.82 to -0.98 ; $P < .001$; $I^2 = 0\%$), and fluticasone (mean change from baseline: -0.74 ; 95% CI, -1.17 to -0.31 ; $P < .001$; $I^2 = 12\%$).

Conclusion. Current evidence supports both efficacy and superiority of combination intranasal azelastine and fluticasone in reducing patient-reported symptom scores in patients with allergic rhinitis. Combination nasal spray should be considered as second-line therapy in patients with allergic rhinitis that is not controlled with monotherapy.

Keywords

allergic rhinitis, azelastine, fluticasone, systematic review

Allergic rhinitis (AR) is a condition that may result from allergen exposure causing IgE-mediated inflammation of the nasal mucosa.¹ Symptomatology varies but often includes sneezing, itchy eyes, watery eyes, nasal congestion, clear rhinorrhea, postnasal drip, and/or facial pressure. These symptoms can have further implications for additional comorbidities, including sinusitis and asthma, as well as have a significant impact on a person's quality of life.² Current recommendations for management of AR emphasize the use of intranasal corticosteroid spray and/or antihistamine medication orally or intranasally.^{3,4} Despite these available therapies, patients often report inadequate symptom relief or difficulty with adherence to therapy.³

A combination intranasal antihistamine and corticosteroid spray represents an alternative therapeutic option for the management of AR. One such formulation is currently available in North America for intranasal use as a combination of azelastine hydrochloride and fluticasone propionate (AzeFlu). This agent is also designated in the literature as MP-AzeFlu or MP29-02 and was originally introduced in the United States under the trade name Dymista (Meda Pharmaceuticals, Somerset, New Jersey). The objective of this systematic review is to examine the current literature to determine if the combination fluticasone-azelastine nasal

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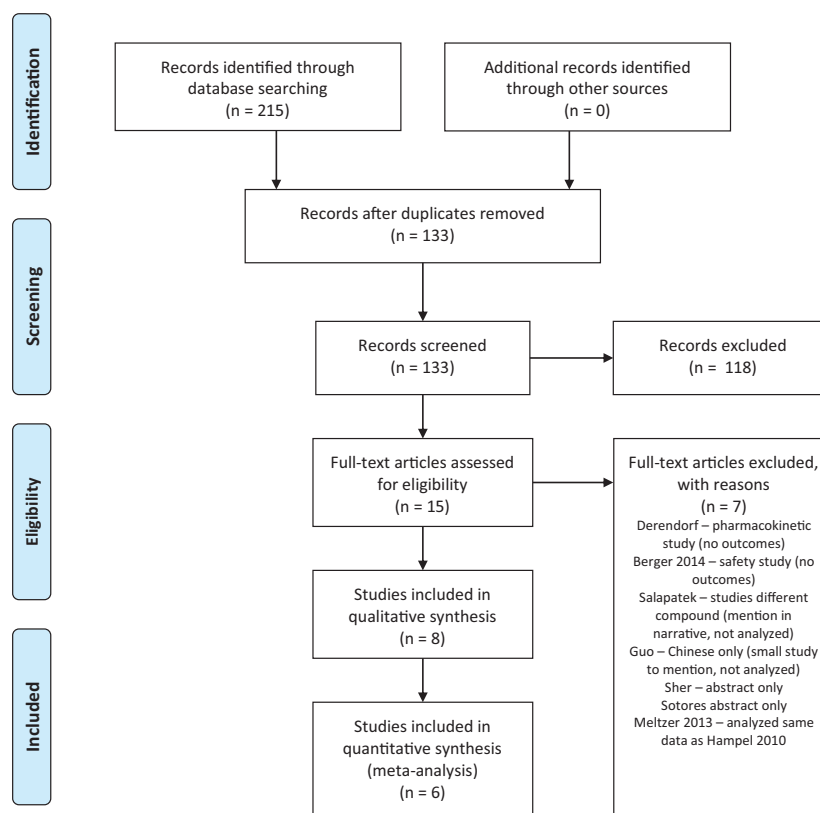


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowsheet of systematic review process.

spray is more effective at treating AR symptoms as opposed to either fluticasone or azelastine as monotherapy alone.

Materials and Methods

A systematic review with meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard⁵ to compare the efficacy of combination intranasal azelastine and fluticasone spray for treatment of AR to that of either azelastine or fluticasone as monotherapy. A comprehensive search of published English-language literature from PubMed, MEDLINE, EMBASE, and Cochrane databases was performed on January 22, 2018. The following keywords were included in the search: *azelastine* and *fluticasone*, or *azeflu*, or *MP29-02*, or *MP-azeflu*, or *dymista*. Date ranges were not applied. Inclusion criteria for the review were defined with the PICOS approach (population, intervention, control, outcome, study design).⁶ Studies were selected in which patient-reported symptom scores of adults or children undergoing treatment with combination intranasal azelastine and fluticasone were compared to those undergoing azelastine, fluticasone, or placebo monotherapies in randomized controlled trials. Unpublished clinical trials, abstracts, non-English articles, and case reports were not included. Two reviewers (P.M.D., E.D.M.) conducted the assessment of the search results. Duplicate results were discarded, and abstracts were screened for study type and interventions in accordance to the PICOS statement. A full-text review of articles with eligible abstracts was then performed, in addition to a manual search of relevant articles in the reference lists.

A standardized data extraction template was used for each study. Information collected included the study type, sample size, inclusion criteria, study sites and dates, lead-in time, study duration, and patient-reported symptom scores, including the Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS), and Rhinitis Quality of Life Questionnaire (RQLQ). Level of evidence of each study was assigned according to the Oxford Centre for Evidence-Based Medicine 2009 criteria.⁷ Using the Cochrane Risk of Bias Tool, random sequence generation, allocation concealment, blinding of participants and outcomes, incomplete outcome data, and selective reporting risks were graded to assess the risk of bias present in each study.

Meta-analysis was performed on studies reporting differences in TNSS change from baseline with standard deviations or confidence intervals for more than 1 treatment group. Three comparisons were of interest: (1) AzeFlu vs azelastine, (2) AzeFlu vs fluticasone, and (3) AzeFlu vs placebo. RevMan 5.3 software (Cochrane Group, London, UK) was used for pooling of data, generation of forest plots, assessment of heterogeneity, and generation of a table summarizing risk of bias.

Results

Systematic Review

The initial database query identified 215 articles, which were screened for relevance to the treatment of AR with combination intranasal azelastine and fluticasone (**Figure 1**). After removal of duplicate records, 133 articles were considered for abstract review. Of these, a total of 15

Table 1. Study Characteristics of Randomized Controlled Trials Comparing Azelastine-Fluticasone Combination Therapy to Monotherapy or Placebo.

Study	Level of Evidence	Number of Patients	Comparisons	Locations	Dates	Duration
Berger et al, 2016 ¹¹	1b	304	AzeFlu vs placebo	35 sites in United States	July 2013–February 2014	14 d
Berger et al, 2016 ¹²	2b	353	AzeFlu vs fluticasone	42 sites in United States	March 2013–October 2013	3 mo
Carr et al, 2012 ⁸ (MP4002)	1b	831	AzeFlu vs azelastine vs fluticasone vs placebo	134 sites in United States	2008-2009	14 d
Carr et al, 2012 ⁸ (MP4004)	1b	776	AzeFlu vs azelastine vs fluticasone vs placebo	134 sites in United States	2008-2009	14 d
Carr et al, 2012 ⁸ (MP4006)	1b	1791	AzeFlu vs azelastine vs fluticasone vs placebo	134 sites in United States	2008-2009	14 d
Hampel et al, 2010 ⁹	1b	607	AzeFlu vs azelastine vs fluticasone vs placebo	6 sites in Texas	January-February 2007	14 d
Laforce et al, 2010 ¹³	1b	135	AzeFlu vs olopatadine + fluticasone	11 sites in United States	March-April 2009	14 d
Meltzer et al, 2012 ¹⁴	1b	776	AzeFlu vs azelastine vs fluticasone vs placebo	41 sites in United States	Fall 2008	14 d
Price et al, 2013 ¹⁵	1b	405	AzeFlu vs fluticasone	37 sites in India	2008-2009	52 wk
Ratner et al, 2008 ¹⁰	1b	150	AzeFlu vs azelastine vs fluticasone	5 sites in Texas	December 2005–February 2006	14 d

articles were included for full-text review. Seven studies were excluded from analysis due to lack of outcomes, insufficient data, reporting of identical clinical trial data, and analysis of different compounds. Manual searching of reference lists resulted in no additional eligible studies. While the remaining 8 articles are included in qualitative analysis, only 4 articles reported data amenable to comparison by meta-analysis.⁸⁻¹¹ Carr et al⁸ included data from three different clinical trials, MP4002, MP4004, and MP4006, each of which was included in meta-analysis. In total, 8 articles were included for systematic review,⁸⁻¹⁵ and 6 clinical trials were used for meta-analysis.

Study characteristics are summarized in **Table 1**. Over 5000 patients were seen at numerous sites across the United States and India. Change in baseline of patient-reported symptom scores was used by each study to measure drug efficacy. All studies used the TNSS, while 3 articles⁹⁻¹¹ reported the RQLQ and 3 articles^{8,9,14} reported the TOSS. Combination AzeFlu was evaluated in each study, with 1 study¹¹ comparing to placebo only, 2 studies^{12,15} comparing to fluticasone only, 1 study¹⁰ comparing to fluticasone and azelastine monotherapy, and 3 articles^{8,9,14} comparing to placebo, fluticasone, and azelastine monotherapy. One study¹³ compared combination AzeFlu to combination olopatadine and fluticasone. Two studies^{11,12} analyzed children between the ages of 6 and 12 years, one of which¹² included patients with a history of AR who were found to benefit from treatment in the opinion of the investigators, whereas all other studies included only patients above the age of 12 years and symptomatic. Inclusion into most studies^{8-11,13,14} required a history of AR with symptoms for at least 2 years and confirmation by positive skin-prick test using local or prevalent seasonal allergens. One study¹⁵ required at least 1 year of symptoms and either a positive skin-prick test or presence of at least 3 symptoms.

A summary of findings for each study is presented in **Table 2**. Presentation of primary efficacy data varied among studies. Some studies^{9,10,13} reported only the change in baseline of patient-reported symptom scores with an associated standard deviation. In these studies, AzeFlu demonstrated a larger magnitude of TNSS reduction compared to either fluticasone or azelastine monotherapy. Others^{8,11,12,14,15} reported efficacy as a difference between change in baseline of the various interventions, with associated confidence intervals and *P* values. These analyses demonstrated significant superiority of AzeFlu in reducing TNSS compared to monotherapy by azelastine, fluticasone, or placebo. Superiority of AzeFlu in reduction of TOSS was statistically significant when compared with placebo but not with azelastine or fluticasone alone.

Data from risk of bias assessment for individual studies are presented in **Figure 2**. The overall level of evidence was 1b, and in general, the included studies all had low risk of selection bias. However, 1 article¹² with level 2b evidence did exhibit high risk of selection, performance, and detection bias.

Meta-Analysis

Meta-analysis was performed on 3 comparisons: combination AzeFlu vs azelastine, AzeFlu vs fluticasone, and

Table 2. Summary of Data.^a

Change in Baseline of Patient-Reported Symptom Scores							
Author, Year	Intervention Analyzed	TNSS, Mean (SD)	TOSS, Mean (SD)	RQLQ, Mean (SD)	TNSS Diff, (95% CI)	TOSS Diff, (95% CI)	RQLQ Diff, (95% CI)
Berger et al, 2016 ¹¹	AzeFlu vs placebo				0.80 (−1.75 to 0.15), <i>P</i> = .099		0.29 (−0.55 to −0.03), <i>P</i> = .027
Berger et al, 2016 ¹²	AzeFlu vs fluticasone				0.14 (−0.28 to −0.01), <i>P</i> = .04		
Carr et al, 2012 ⁸ (MP4002)	AzeFlu vs azelastine				−1.14 (−2.22 to −0.54), <i>P</i> = .002	−0.25 (−0.90 to 0.41), <i>P</i> = .457	
Carr et al, 2012 ⁸ (MP4004)	AzeFlu vs fluticasone				−0.90 (−1.74 to −0.07), <i>P</i> = .034	−0.52 (−1.14 to 0.10), <i>P</i> = .097	
	AzeFlu vs placebo				−2.7 (−3.48 to −1.91), <i>P</i> < .001	−1.17 (−1.77 to −0.57), <i>P</i> < .001	
	AzeFlu vs azelastine				−1.0 (−1.90 to −0.09), <i>P</i> = .032	−0.6 (−1.25 to 0.05), <i>P</i> = .069	
Carr et al, 2012 ⁸ (MP4006)	AzeFlu vs fluticasone				−1.0 (−1.91 to −0.05), <i>P</i> = .038	−0.88 (−1.54 to −0.23), <i>P</i> = .009	
	AzeFlu vs placebo				−2.5 (−3.33 to −1.67), <i>P</i> < .001	−1.54 (−2.16 to −0.92), <i>P</i> < .001	
	AzeFlu vs azelastine				−0.70 (−1.30 to −0.13), <i>P</i> = .029	−0.03 (−0.47 to 0.42), <i>P</i> = .912	
Hampel et al, 2010 ⁹	AzeFlu vs fluticasone				−0.60 (−1.22 to −0.07), <i>P</i> = .016	−0.26 (−0.69 to 0.18), <i>P</i> = .247	
	AzeFlu vs placebo				−2.70 (−2.70 to −1.57), <i>P</i> < .001	−1.07 (−1.50 to −0.64), <i>P</i> < .001	
	AzeFlu	−5.31 (5.08), <i>P</i> < .001	−3.33	1.6, <i>P</i> < .001			
Laforce et al, 2010 ¹³	Azelastine	−3.25 (4.16), <i>P</i> < .001	−2.62	1.17, <i>P</i> < .001			
	Fluticasone	−3.84 (4.76), <i>P</i> < .001	−2.17	1.43, <i>P</i> < .001			
	Placebo	−2.2	−1.32	1.01			
	AzeFlu	−4.15 (2.63)					
Meltzer et al, 2012 ¹⁴	Combination nasal spray	−4.28 (2.63)					
	olopatadine + fluticasone						
	AzeFlu vs azelastine				−1.0 (−1.90 to −0.09), <i>P</i> = .032	−0.6 (−1.25 to 0.05), <i>P</i> = .069	
	AzeFlu vs fluticasone				−0.99 (−1.91 to 0.05), <i>P</i> = .038	−0.88 (−1.54 to −0.23), <i>P</i> = .009	
Price et al, 2013 ¹⁵	AzeFlu vs placebo				−2.51 (−3.33 to −1.67), <i>P</i> < .001		
	AzeFlu vs fluticasone				28 wk: −0.35 (−0.59 to −0.11), <i>P</i> = .0048 52 wk: −0.27 (−0.56 to 0.02), <i>P</i> = .064		
Ratner et al, 2008 ¹⁰	AzeFlu	−7.4 (5.6)		1.92 (1.46)			
	Azelastine	−4.8 (4.3)		1.21 (1.02)			
	Fluticasone	−5.2 (4.6)		1.47 (1.21)			

Abbreviations: AzeFlu, combination nasal spray azelastine + fluticasone; CI, confidence interval; RCT, randomized clinical trial; RQLQ, Rhinitis Quality of Life Questionnaire; SD, standard deviation; TNSS, Total Nasal Symptom Score; TNSS diff, difference in posttreatment symptom scores; TOSS, Total Ocular Symptom Score.

^aNegative change in baseline of TNSS/TOSS favors combination AzeFlu. Positive change in baseline of RQLQ favors combination AzeFlu.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Berger 2016	+	+	+	+	-	-
Berger 2016 2b	+	-	-	-	+	+
Carr 2012a	+	+	+	+	+	+
Carr 2012b	+	+	+	+	+	+
Carr 2012c	+	+	+	+	+	+
Hampel 2010	+	?	?	?	-	+
LaForce 2010	+	?	?	?	+	+
Meltzer 2012	+	+	+	+	-	+
Price 2013	+	?	?	?	+	-
Ratner 2008	+	+	+	+	+	+

Figure 2. Itemized assessment of the risk of bias.

AzeFlu vs placebo. Limited by data reporting in the articles, only TNSS scores of 6 studies⁸⁻¹¹ were suitable for meta-analysis. AzeFlu was favored over fluticasone monotherapy with a mean change in baseline of -0.74 (95% confidence interval [CI], -1.17 to -0.31 ; $P < .001$; $I^2 = 12\%$; **Figure 3**). AzeFlu was also favored over azelastine monotherapy with a mean change in baseline of -1.40 (95% CI, -1.82 to -0.98 ; $P < .001$; $I^2 = 0\%$; **Figure 4**). Finally, AzeFlu was favored over placebo with a mean change in baseline of -2.41 (95% CI, -2.82 to -1.99 ; $P < .001$; $I^2 = 60\%$; **Figure 5**).

Discussion

This systematic review identified 8 eligible articles that reported the effect of combination AzeFlu on reducing patient-reported symptom scores in patients with AR. All but 1 article recognized AzeFlu as the superior treatment with a greater reduction of TNSS than with fluticasone,

azelastine, or placebo monotherapy. In the article that did not demonstrate superiority of AzeFlu, younger children were subject to caretaker assessment symptom scores, which may have misrepresented baseline symptoms and subsequent change. However, with subgroup analysis of children reporting their own symptoms, TNSS was seen to be significantly reduced with use of AzeFlu vs placebo ($P = .002$). While our review focuses on the efficacy of AzeFlu, some studies suggest different combinations of antihistamine and corticosteroids that may be efficacious in managing AR.^{13,16}

Meta-analysis demonstrated superiority of AzeFlu over monotherapy with either medication alone. Meta-analysis was limited to 4 randomized controlled trials (RCTs)⁷⁻¹⁰ that reported change of symptom score from baseline for each medication. Articles that reported a “TNSS diff” comparing different treatment groups were excluded due to inadequate information for meta-analysis. Our meta-analysis was limited to only nasal symptoms quantified with TNSS, as not all studies captured in systematic review reported TOSS.

The International Consensus Statement on Allergy and Rhinology and the American Academy of Otolaryngology–Head and Neck Surgery Foundation Clinical Practice Guideline for Allergic Rhinitis both recommend a first-line treatment of intranasal steroid spray and suggest clinicians may offer combination therapy in patients with persistent symptoms.^{1,17} The American College of Allergy Asthma and Immunology reported that 52% of allergists and 39% of primary care physicians prescribe more than 1 oral antihistamine, with 75% of those physicians citing inadequate symptom relief as the rationale for prescribing multiple drugs.¹⁸ Because adherence to AR treatment has been reported to be around 50%, and polypharmacy is known to further decrease adherence, combination medications in a single delivery system may be helpful to negate these effects.^{19,20}

Overall, the quality of evidence included in this study was high, with only 1 article¹² having a level of evidence lower than 1b; this was primarily a safety study in which efficacy was assessed only secondarily. A limitation to our analysis is that only 2 included studies^{12,15} measured symptom scores beyond the 2-week period, making conclusions of long-term effectiveness difficult to make. However, these 2 studies demonstrated superior efficacy of AzeFlu at timepoints ranging from 12 to 52 weeks after initiation of treatment.^{12,15}

Benefits of the combination nasal spray include rapid onset and more effective relief of multiple symptoms than either intranasal monotherapy. There is a preponderance of benefit over harm considering the low risk of serious adverse effects. Barriers to use of this medication include patient tolerance, especially due to taste, and cost. AzeFlu can pose a moderate financial burden, as the average wholesale price of one 23-g bottle (a 1-month supply) was \$202 in 2016. These factors can limit the accessibility of combination therapy as a routine first-line treatment for AR. However, based on results in this review, we recommend that combination therapy with intranasal corticosteroid and intranasal antihistamine may be used as second-line therapy

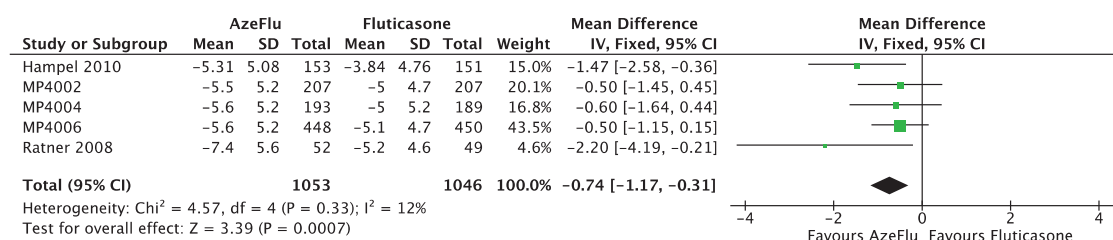


Figure 3. Change in Total Nasal Symptom Score after treatment with AzeFlu vs fluticasone monotherapy.

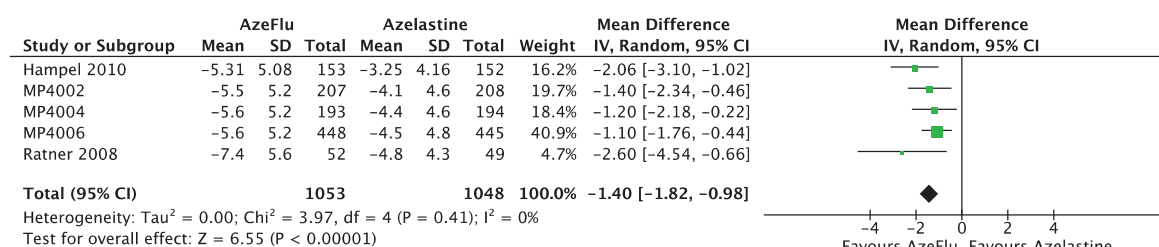


Figure 4. Change in Total Nasal Symptom Score after treatment with AzeFlu vs azelastine monotherapy.

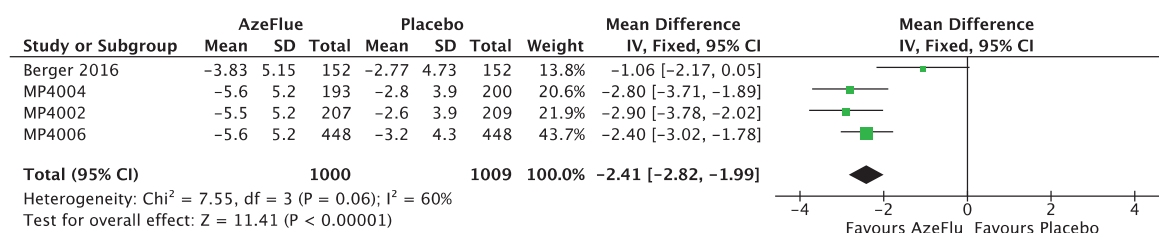


Figure 5. Change in Total Nasal Symptom Score after treatment with AzeFlu vs placebo.

in the treatment of AR when initial monotherapy with either intranasal corticosteroid or antihistamine does not provide adequate symptom control.

Conclusion

Combination therapy with azelastine and fluticasone nasal spray produces relief of nasal symptoms that is superior to monotherapy with either agent alone. AzeFlu should be considered as second-line therapy for patients with AR that is not controlled with monotherapy.

Author Contributions

Peter M. Debbaneh, data acquisition, drafting manuscript, final approval, accountable for all aspects; **Anna K. Bareiss**, data interpretation, revising manuscript, final approval, accountable for all aspects; **Sarah K. Wise**, study conception, revising manuscript, final approval, accountable for all aspects; **Edward D. McCoull**, study design, data acquisition, data interpretation, revising manuscript, final approval, accountable for all aspects.

Disclosures

Competing interests: Edward D. McCoull, consultant (Acclarent); Sarah K. Wise, Scientific Advisory Board (OptiNose, SinopSys Surgical, NeurENT), consultant (Stryker).

Sponsorships: None.

Funding source: None.

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