Pharmacologic Treatment of Seasonal Allergic Rhinitis: Synopsis of Guidance From the 2017 Joint Task Force on Practice Parameters

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Description: The Joint Task Force on Practice Parameters, which comprises representatives of the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), formed a workgroup to review evidence and provide guidance to health care providers on the initial pharmacologic treatment of seasonal allergic rhinitis in patients aged 12 years or older.

Methods: To update a prior systematic review, the workgroup searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 18 July 2012 to 29 July 2016 to identify studies that addressed efficacy and adverse effects of single or combination pharmacotherapy for seasonal allergic rhinitis. In conjunction with the Joint Task Force, the workgroup reviewed the evidence and developed recommendations about initial treatment approaches by using the Grading of Recommendations Assessment, Development and Evaluation approach. Members of the AAAAI, the ACAAI, and the general public provided feedback on the draft document, which the Joint Task Force reviewed before finalizing the guideline.

Seasonal allergic rhinitis, which affects up to 14% of the U.S. adult population, is managed by clinicians and patients using a combination of prescription and over-the-counter medications. Most patients who consult an allergy and immunology specialist have already tried many over-the-counter monotherapies without success and are seeking more effective treatment. No consensus exists about whether a particular medication should be used for initial treatment or about the benefit of using 2 or more medications concurrently for initial treatment. This synopsis of a 2017 guideline from the Joint Task Force on Practice Parameters addresses specific recommendations regarding initial pharmacotherapy approaches for patients aged 12 years or older with seasonal allergic rhinitis. Three key questions were addressed in this evidence-based guideline, which was developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method. Allergen avoidance, which can be effective for indoor allergens, is usually inadequate for the outdoor allergens that cause and perpetuate symptoms in patients with seasonal allergic rhinitis. Many patients with moderate-to-severe seasonal allergic rhinitis may benefit from specific allergen immunotherapy (subcutaneous or sublingual), which is the only disease-modifying therapeutic method (1, 2). These management interventions and pharmacotherapy for perennial allergic rhinitis were not addressed in this guideline.

Recommendation 1: For initial treatment of seasonal allergic rhinitis in persons aged 12 years or older, routinely prescribe monotherapy with an intranasal corticosteroid rather than an intranasal corticosteroid in combination with an oral antihistamine. (Strong recommendation)

Recommendation 2: For initial treatment of seasonal allergic rhinitis in persons aged 15 years or older, recommend an intranasal corticosteroid over a leukotriene receptor antagonist. (Strong recommendation)

Recommendation 3: For treatment of moderate to severe seasonal allergic rhinitis in persons aged 12 years or older, the clinician may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine for initial treatment. (Weak recommendation)

Guideline Development and Review Process

The Joint Task Force on Practice Parameters formed a workgroup, comprising volunteers from the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), to find and critique evidence relevant to pharmacotherapy for seasonal allergic rhinitis. Three patient advocates were invited to participate in the development of the final recommendations. All workgroup members disclosed potential conflicts of interest in accordance with the standards of the National Academy of Sciences (3). The workgroup developed a list of clinical questions about the use of single or combination medications for seasonal allergic rhinitis. From these, 3 key questions were chosen as the focus of a systematic review. Of note, the 3 questions were also part of a large systematic review on allergic rhinitis that was funded by the Agency for Healthcare Research and Quality (AHRQ) and published in 2013 (4). The AHRQ review was limited to randomized controlled trials of persons aged 12 years or older with seasonal allergic rhinitis of at least 2 weeks’ duration during an active pollen season. The workgroup updated the searches used in the AHRQ review (MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials) from 18 July 2012 to 29 July 2016 and found no additional randomized trials of medication therapy for seasonal allergic rhinitis.
The workgroup and the Joint Task Force reviewed the quality of the published trials; contacted authors, when possible, for any missing information; evaluated the clinical significance of reported patient-important outcomes; and determined the overall quality of evidence across outcomes. The certainty of the body of evidence, using GRADE quality analysis and evaluating for inconsistency, indirectness, and imprecision, was defined as high, moderate, low, or very low (5). Before determining the final recommendation or suggestion for an intervention, the Joint Task Force considered safety, cost, and patient preference. These considerations were based on experience and were informed by an informal review of the literature. The guideline was externally reviewed by the AAAAI and the ACAAI, by both appointed official reviewers and members at large. The document was posted on the Joint Task Force Web site (www.allergyparameters.org) for general public review. All comments that were received were reviewed by the Joint Task Force, revisions were incorporated, and general feedback was provided to reviewers. The final guideline and appendices are published in the Annals of Allergy, Asthma, & Immunology and are posted at www.allergyparameters.org (6).

**Recommendations**

1. For initial treatment of seasonal allergic rhinitis in persons aged 12 years or older, routinely prescribe monotherapy with an intranasal corticosteroid rather than an intranasal corticosteroid in combination with an oral antihistamine. (Strong recommendation)

   Eight trials addressed whether using a combination of an oral antihistamine and an intranasal corticosteroid has greater clinical benefit than using an intranasal corticosteroid alone (7–14), but only 5 trials reported data that could be analyzed (7–11). All 5 evaluated nasal symptoms as the main outcome, 3 reported ocular symptoms (8, 9, 11), and 1 reported quality of life as a primary end point (10). For measurement of nasal symptoms, 3 studies (8, 10, 11) used the Total Nasal Symptom Score (TNSS), which measures nasal congestion, sneezing, rhinorrhea, and nasal itching (discussed earlier) (18); a score of 0 to 400 on a visual analogue scale (discussed earlier) (15, 16, 19); or a Composite Symptom Score of 0 to 4 (20). Three of these studies included a placebo group (18–20), and 2 used a parallel-treatment design (15, 16). For inclusion, 3 studies required a visual analogue scale score of 200 out of 400 for nasal symptom severity (15, 16, 19), and 2 trials (18, 20) did not require any degree of nasal symptom severity.

   Although there is no consensus in the literature about thresholds for a minimal clinically important difference between treatments, the workgroup and the Joint Task Force determined that the reductions in nasal symptoms reported in the trials comparing an intranasal corticosteroid versus montelukast were clinically meaningful according to recently published criteria (21). Some patients do not tolerate or accept the use of an intranasal corticosteroid and prefer an oral agent, such as montelukast, despite its lesser efficacy (22, 23).

   In patients with a concurrent diagnosis of mild persistent asthma, a leukotriene receptor antagonist may be prescribed and may also provide benefit for seasonal

 treatment (7, 11), 2 used a parallel-treatment design (8, 9), and 1 used a crossover design (10).

   Overall, we judged the evidence as not proving a benefit of adding an oral antihistamine to an intranasal corticosteroid and recognized that oral antihistamines, mainly first-generation, may cause sedation and other adverse effects. Five trials (11, 15–17) disclosed and met the sample size needed to determine statistically significant findings, whereas the remaining studies either did not report this value or did not obtain the needed study participants; none of the trials used the concept of minimal clinically important difference to power the study. Although participants in these trials were recruited on the basis of meeting criteria for seasonal allergic rhinitis and reaching a threshold of nasal symptoms, they were not randomly assigned on the basis of treatment failure despite regular use of an intranasal corticosteroid. Because there may be a subgroup of patients who experience treatment failure with an intranasal corticosteroid alone and could benefit from the addition of an oral antihistamine, these data do not permit determination of whether adding an oral antihistamine would benefit patients with residual symptoms despite appropriately dosed intranasal corticosteroids.

2. For initial treatment of seasonal allergic rhinitis in persons aged 15 years or older, recommend an intranasal corticosteroid over a leukotriene receptor antagonist. (Strong recommendation)

   Five trials addressed the relative efficacy of a leukotriene receptor antagonist (such as oral montelukast) compared with an intranasal corticosteroid (15, 16, 18–20). Overall, we judged the evidence as clearly showing that an intranasal corticosteroid was more effective than montelukast for nasal symptom reduction, although in 1 study (19), the numerically greater improvement in symptom-free days did not reach statistical significance. The primary end points were the participant-rated TNSS incorporating nasal congestion, rhinorrhea, sneezing, and nasal itching (discussed earlier) (18); a score of 0 to 400 on a visual analogue scale (discussed earlier) (15, 16, 19); or a Composite Symptom Score of 0 to 4 (20). Of 3 of these studies included a placebo group (18–20), and 2 used a parallel-treatment design (15, 16). For inclusion, 3 studies required a visual analogue scale score of 200 out of 400 for nasal symptom severity (15, 16, 19), and 2 trials (18, 20) did not require any degree of nasal symptom severity.
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...allergic rhinitis; however, this would not be the preferred agent for a patient with either condition (24). Finally, there may be subgroups of patients with seasonal allergic rhinitis who are more responsive to a leukotriene receptor antagonist, as in the case of asthma (25).

3. For treatment of moderate to severe seasonal allergic rhinitis in persons aged 12 years or older, the clinician may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine for initial treatment. (Weak recommendation)

The 2008 update of the Joint Task Force’s rhinitis practice parameter (26) recommended intranasal corticosteroids as the most effective medication class for controlling symptoms, as did the original practice parameter from 1998 (27). Intranasal antihistamines, which are generally less effective than intranasal corticosteroids, were suggested as an alternative for first-line treatment of allergic and nonallergic rhinitis. The 2008 document also stated that, on the basis of limited data reporting an additive benefit, concomitant administration of an intranasal antihistamine and an intranasal corticosteroid in separate devices could be considered.

Five trials published since 2008 have addressed the relative efficacy of combination therapy with an intranasal antihistamine and an intranasal corticosteroid compared with monotherapy with either agent for initial treatment of nasal symptoms in persons aged 12 years or older with seasonal allergic rhinitis (17, 28–30). Four studies compared fluticasone propionate alone versus fluticasone propionate (200 mcg) plus azelastine (548 mcg) as a single combination spray (17, 28, 30). The fifth study compared fluticasone propionate alone versus fluticasone propionate plus azelastine, 1100 mcg daily, administered using 2 separate commercially available sprays (29). Three trials included a placebo group (17, 28, 30), and 1 used a parallel-treatment design (29). All studies required a reflective 12-hour TNSS of 8 out of 12, and 3 studies (17, 29, 30) required a congestion score of 2 or 3 for inclusion. All studies used a reflective 12-hour morning and evening TNSS (0 to 12 for each, for a total score of 0 to 24 per day). A review of the absolute nasal symptom reduction in 3 studies (17, 28, 30) showed that all participants had a TNSS of 18.1 to 19.0 out of 24 at baseline; after treatment, the reductions in symptom scores were −2.2 to −3.03 for placebo, −3.25 to −4.54 for azelastine, −3.04 to −5.1 for fluticasone propionate, and −5.31 to −5.7 for fluticasone propionate plus azelastine. The fourth study (29) used the method of least squares and found symptom reductions of 24.8% for azelastine, 29.1% for fluticasone propionate, and 37.9% for fluticasone propionate plus azelastine. The authors calculated that the absolute improvements represented greater than 40% relative improvement for the use of fluticasone propionate plus azelastine than with either agent alone (29). In all 4 studies, fluticasone propionate plus azelastine showed the greatest symptom reduction, followed by fluticasone propionate, azelastine, and placebo.

The workgroup and the Joint Task Force concluded that for the primary end point of TNSS, the observed differences were clinically meaningful (21). However, for quality of life, assessed with the Rhinitis Quality of Life Questionnaire and with a threshold of 0.5 for the minimal clinically important difference, we found that combination therapy did not consistently exceed the minimal clinically important difference compared with monotherapies. Combination therapy improved overall ocular symptoms compared with either monotherapy but reached a statistically significant difference only when compared with fluticasone propionate (17, 28, 30). The rate of adverse events in the 5 studies was low. Dysgeusia, the most common adverse event, was reported in all studies, and incidence varied from 2.1% to 13.5% of participants and was higher in the azelastine group in 2 studies (17, 28) and in the group receiving fluticasone propionate plus azelastine in 2 studies (29, 30). Occurrence of epistaxis in all treatment groups was similar to or lower than in the placebo groups in all studies. Somnolence, which was reported in 2 of 6 studies, varied from 0.4% to 1.1% in the treatment groups that included azelastine, similar to what has been reported in other clinical trials (31).

Finally, the evidence analyzed for key question 3 showed that the addition of an intranasal antihistamine to an intranasal corticosteroid in patients with moderate-to-severe seasonal allergic rhinitis provides additional benefit, in contrast to combination therapy with an intranasal corticosteroid and an oral antihistamine (key question 1). Unlike recommendations 1 and 2, which were graded as strong, the Joint Task Force graded recommendation 3 as weak. This was based on several factors, including concerns about potential bias in the available studies, a lack of studies that addressed add-on therapy rather than starting with 1 or 2 drugs, and consideration of the greater potential for untoward effects and the added cost of using a second medicine.

COMPARISON OF EVIDENCE-BASED GUIDELINES ON ALLERGIC RHINITIS

The current guideline is 1 of 4 major allergic rhinitis documents published since 2013 that used an evidence-based approach. The other 2 guidelines were the 2015 clinical practice guideline on allergic rhinitis from the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (32) and the 2016 revision of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (33). A comparative effectiveness review was also completed by the AHRQ in 2013 (4).

The first question, which explored adding an oral antihistamine to an intranasal corticosteroid for the initial treatment of seasonal allergic rhinitis, was addressed in all 4 documents. The reference articles evaluated by these 4 groups were almost identical. Both the Joint Task Force and the AAO-HNS concluded that there was no benefit of adding an oral antihistamine to an intranasal corticosteroid, whereas ARIA found the combination to be equivalent but an option for initial
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The quality of the evidence was judged to be moderate by the Joint Task Force, weak by ARIA, and insufficient to make a determination by the AHRQ and was not addressed by the AAO-HNS. The recommendation was rated as strong by the Joint Task Force and weak by ARIA and was not rated by the AHRQ or the AAO-HNS.

The second question, which involved comparison of an intranasal corticosteroid versus a leukotriene receptor antagonist for the initial treatment of seasonal allergic rhinitis, was addressed in only 3 of the 4 documents. The Joint Task Force found high-quality evidence that intranasal corticosteroids were more effective than leukotriene receptor antagonists and issued a strong recommendation, whereas the AHRQ, using the same references, concluded that the agents were equivalent, with good- to poor-quality evidence and a strong recommendation. The AAO-HNS determined that intranasal corticosteroids were more effective but did not rate the quality of the evidence or the strength of the recommendation. The 2010 ARIA guideline addressed this question and found low-quality evidence that intranasal corticosteroids were more effective but issued a strong recommendation (33).

The third question, which compared the effectiveness of monotherapy with an intranasal corticosteroid or an intranasal antihistamine versus the combination of these agents for initial treatment of seasonal allergic rhinitis, was addressed in all 4 documents. The Joint Task Force (strong quality of evidence and weak recommendation) and the AAO-HNS (no grading of evidence or strength of recommendation) concluded that the combination was more effective than either monotherapy. The AHRQ (low-quality evidence and strong recommendation) determined that monotherapy with either agent was as effective as combination therapy. ARIA stated that adding an intranasal antihistamine to an intranasal corticosteroid did not improve efficacy to a meaningful degree compared with monotherapy with an intranasal corticosteroid (moderate-quality evidence and weak recommendation); however, the combination was judged to be more effective than monotherapy with an intranasal antihistamine (low-quality evidence and weak recommendation). These inconsistent recommendations may have resulted from guideline groups prioritizing various factors (such as efficacy measures, relative benefits, adverse effects, patient acceptance, and cost) differently when comparing therapeutic interventions. Our weak recommendation for combination therapy was based on concerns about potential bias in the critically appraised studies and the greater potential for adverse effects associated with combination therapy, including dysgeusia and somnolence. The weak recommendation implies that most patients would wish to receive the combination, but many would not want to receive it.

Although objective measures are ideal for assessing outcomes in many diseases, for rhinitis the subjective, patient-reported TNSS is the U.S. Food and Drug Administration’s preferred measure for determining drug efficacy. Although the TNSS is currently the best tool available, it may not take into consideration all of the elements that would constitute an improved quality of life for patients with rhinitis. One major obstacle in comparing the efficacy of treatment approaches in seasonal allergic rhinitis is the lack of rigorous clinical trials that have adequately defined a benchmark threshold for a minimal clinically important difference for meaningful improvement in TNSS. There currently is no universal agreement on the minimum reduction in TNSS that should be considered clinically meaningful, given that this value varies on the basis of whether one is using the “distribution-based” approach (a statistically derived method) or the “anchor-based” approach (a method that relates symptom reduction to a patient-related score of well-being) (21, 34, 35). Although not all guideline writing groups apply a minimal clinically important difference when evaluating outcomes of treatment trials, those that do often use different methods.

Consequently, guideline groups can review the same data but reach different conclusions about the comparative effectiveness of treatments for seasonal allergic rhinitis that, in turn, can result in divergent recommendations (21). When treating patients with seasonal allergic rhinitis, clinicians need to use their expertise to assist patients in evaluating the best treatment choice through shared decision making; consider the potential for benefit as well as the potential for harm, the burden, and the cost of combination therapy; and allow patients to express their values and preferences and participate in the decision-making process.

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References

1. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a parameter practice third update. J Allergy Clin Immunol. 2011;127:S1-55. [PMID: 21122901] doi:10.1016/j.jaci.2010.09.034
2. Greenhawt M, Oppenheimer J, Nelson M, Nelson H, Lockey R, Lieberman P, et al. Subcutaneous allergen immunotherapy practice parameter update. Ann Allergy Asthma Immunol. 2017;118:276-82. [PMID: 28284533] doi:10.1016/j.anai.2016.12.009
3. The National Academies of Sciences, Engineering, and Medicine. Conflicts of interest policy for committees used in the development of reports. 12 May 2003. Accessed at www.nationalacademies.org/coi on 26 September 2017.
4. Glacy J, Putnam K, Godfrey S, Falzon L, Mauger B, Samson D, et al. Treatments for Seasonal Allergic Rhinitis. Comparative Effectiveness Review no. 120. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Evidence-Based Practice Center under contract no. 290-2007-10058-I.) AHRQ publication no. 13-EHC098-ER. Rockville: Agency for Healthcare Research and Quality; July 2013. Accessed at https://effectivenesshealthcare.ahrq.gov/ehc/products/376/1588/allergy-seasonal-report-130711.pdf on 26 September 2017.
5. Brozek JL, Aiki EA, Alonzo-Coello P, Lang D, Jaeschke R, Williams JW, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64:669-77. [PMID: 19210357] doi:10.1111/j.1399-3003.2009.01973.x
6. Dykewicz MS, Wallace DV, Baroody F, Bernstein J, Craig T, Finegold I, et al. Treatment of seasonal allergic rhinitis. An evidence-based focused 2017 guideline update. Ann Allergy Asthma Immunol. 2017. [Epub ahead of print] doi:10.1016/j.anai.2017.08.012
7. Ratner PH, van Bavel JH, Martin BG, Hampel FC Jr, Howland WC 3rd, Rogenes PR, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. J Fam Pract. 1994;47:118-25. [PMID: 9722799]
8. Di Lorenzo G, Pacor ML, Pellitteri ME, Morici G, Di Gregoli A, Lo Bianco C, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. Clin Exp Allergy. 2004;34:259-67. [PMID: 14987306]
9. Benincasa C, Lloyd R. Evaluation of fluticasone propionate aqueous nasal spray alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. Drug Investigation. 1994;8:225-32.
10. Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. Clin Exp Allergy. 2006;36:676-84. [PMID: 16650054]
11. Anolik R; Metametason Furoate Nasal Spray With Loratadine Study Group. Clinical benefits of combination treatment with metametason furoate nasal spray and loratadine vs monotherapy with metametason furoate in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100:264-71. [PMID: 18426147] doi: 10.1016/S1081-2016(08)00452-8
12. Can D, Tanaç R, Demir E, Gülen F, Veral A. Is the usage of intra-nasal glucocorticosteroids alone in allergic rhinitis sufficient? Allergy Asthma Proc. 2006;27:248-53. [PMID: 16913269]
13. Modgil V, Badyl DK, Verghese A. Efficacy and safety of montelukast add-on therapy in allergic rhinitis. Methods Find Exp Clin Pharmacol. 2010;32:669-74. [PMID: 21225018] doi:10.1385/mfe:2010.32.9.1533686
14. Brooks C, Francom S, Peel B, Chene B, Klett K. Spectrum of seasonal allergic rhinitis symptom relief with topical corticoid and oral antihistamine given singly or in combination. Am J Rhinol. 1996;10:193-9. doi:10.2500/105065896781794941
15. Martin BG, Andrews CP, van Bavel JH, Hampel FC, Klein KC, Prillaman BA, et al. Comparison of fluticasone propionate aqueous nasal spray and oral montelukast for the treatment of seasonal allergic rhinitis symptoms. Ann Allergy Asthma Immunol. 2006;96:851-7. [PMID: 16802774]
16. Ratner PH, Howland WC 3rd, Arastu R, Philpot EE, Klein KC, Baidoo CA, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. Ann Allergy Asthma Immunol. 2003;90:536-42. [PMID: 12775135]
17. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012;129:128-22. [PMID: 22418065] doi:10.1016/j.jaci.2012.01.077
18. Pullerits T, Praks L, Ristioja V, Lövttal J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol. 2002;109:949-55. [PMID: 12063523]
19. Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. Chest. 2005;128:1910-20. [PMID: 16236835]
20. Lu S, Malice MP, Dass SB, Reiss TF. Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. J Asthma. 2009;46:878-83. [PMID: 19905912] doi:10.3109/02786129.200903104540
21. Meltzer EO, Wallace D, Dykewicz M, Shneyer L. Minimal clinically important difference (MCID) in allergic rhinitis: Agency for Healthcare Research and Quality or anchor-based thresholds? J Allergy Clin Immunol Pract. 2016;4:682-8. [PMID: 27084419] doi:10.1016/j.jaip.2016.02.006
22. Hellings PW, Dobbels F, Denhaerynck K, Piessens M, Ceuppens JL, De Geest S. Explorative study on patient’s perceived knowledge level, expectations, preferences and fear of side effects for treatment for allergic rhinitis. Clin Transl Allergy. 2012;2:9. [PMID: 22643067]
23. Forbes Consulting Group. Understanding the Dynamics Surrounding Allergy Suffering and Treatment. Lexington, MA: Forbes Consulting Group; 2005.
24. National Asthma Education and Prevention Program; Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Report no. 07-4051. Bethesda: National Heart, Lung, and Blood Institute; 2007. Accessed at www.ncbi.nlm.nih.gov/books/NBK7232 on 29 July 2017.
25. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RS, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol. 2005;115:233-42. [PMID: 15696016] doi:10.1016/j.jaci.2002.01.077
26. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al; Joint Task Force on Practice. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008;122:S1-84. [PMID: 18662584] doi:10.1016/j.jaci.2008.06.003
27. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol. 1998;81:478-518. [PMID: 9860027]
28. Meltzer EO, LaForce C, Ratner P, Price D, Ginsberg D, Carr W, MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy
and safety. Allergy Asthma Proc. 2012;33:324-32. [PMID: 22856633] doi:10.2500/aap.2012.33.3587

29. Ratner PH, Hampel F, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100:74-81. [PMID: 18254486] doi:10.1016/S1081-1206(10)60408-5

30. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010;105:168-73. [PMID: 20674829] doi:10.1016/j.anai.2010.06.008

31. Meda Pharmaceuticals. DYMISTA full prescribing information. Updated 16 May 2017. Accessed at https://docs.google.com/viewer?url=http%3A%2F%2Fdymista.com%2Fpdf%2FDymistaUSPI.pdf on 26 September 2017.

32. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis executive summary. Otolaryngol Head Neck Surg. 2015;152:197-206. [PMID: 25645524] doi:10.1177/0194599814562166

33. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. J Allergy Clin Immunol. 2017;140:950-8. [PMID: 28602936] doi:10.1016/j.jaci.2017.03.050

34. Devillier P, Chassany O, Vicaut E, de Beaumont O, Robin B, Dreyfus JF, et al. The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. Allergy. 2014;69:1689-95. [PMID: 25155425] doi:10.1111/all.12518

35. Barnes ML, Vaidyanathan S, Williamson PA, Lipworth BJ. The minimal clinically important difference in allergic rhinitis. Clin Exp Allergy. 2010;40:242-50. [PMID: 19895590] doi:10.1111/j.1365-2222.2009.03381.x
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