

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.

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)

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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.

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, each rated on a 4-point Likert scale of 0 to 3 (0 indicates no symptoms, 1 indicates mild symptoms, 2 indicates moderate symptoms, and 3 indicates severe symptoms) and summed for a total score of 0 to 12. A study that reported on the same 4 nasal symptoms (7) used a visual analogue scale of 0 to 100 for each symptom, for a maximum score of 400, and the remaining study (9) used a scale of 0 to 9 for combined nasal symptom severity. Inclusion criteria included a TNSS of 6 or higher and a congestion score of 2 or higher (11), a score of 200 or higher on a visual analogue scale of 0 to 400 (7), and the presence of at least 1 of 4 nasal symptoms plus headache or 1 additional symptom involving the nose or eyes (9). One study did not require a specific nasal symptom severity score, but the mean TNSS reported at baseline was 4.56 (95% CI, 3.61 to 5.50) (10). Two trials included a placebo group receiving no

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). 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

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, -3.84 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

treatment. 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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