placebo in children 6 to 11 years old.[461] Its superior efficacy in reducing the PM 12 hour-reflective (daytime) total nasal symptom score over intranasal fluticasone was also demonstrated over the whole range of a 12-month randomized, open-label trial in patients with chronic rhinitis (PAR and NAR), although no NAR-subgroup analysis was presented.[462] A 6-week randomized trial of 162 patients with NAR demonstrated significantly greater ($P < .01$) reduction in nasal obstruction score with the combination of an INCS and an INAH compared with monotherapy with an INCS.[463]

However, as reviewed in the 2017 rhinitis GRADE document,[174] all these studies were designed to compare the use of combination therapy versus monotherapy as initial treatment of SAR and not as add-on therapy. The JTFPP recognizes that in clinical practice, in most cases, the combination will be used when monotherapy has failed to relieve symptoms in patients with SAR, PAR, and NAR in all ages for which the product has been approved. However, for PAR and NAR, the recommendations are based predominantly on expert opinion.

MP29-02 contains a combination of 2 active substances, fluticasone propionate and azelastine. Slightly higher fluticasone area under the curve (AUC) $_{0\text{-tlast}}$ and C_{max} have been reported compared with those of commercially available intranasal fluticasone propionate.[464] Of note are the safety data reported from the above-mentioned 12-month trial, with MP29-02 1 spray per nostril twice a day, in which 8 of 404 patients were discontinued at 6 months, because of an adverse event (3 decreased serum cortisol, 3 cataract, 2 acne) versus 1 of 207 in the commercially available fluticasone group (cataract).[462,465] Other additional combination devices, currently not FDA-approved, including those that contain different INCS and INAH, have been studied.[466-472] Several of these studies confirm additive benefit over intranasal monotherapies.

INCS with intranasal ipratropium for control of rhinorrhea

Recommendation 25. *CBS:* We suggest that for patients taking an INCS who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium.

Strength of the recommendation: Conditional

Certainty of evidence: Moderate

In patients with rhinorrhea not fully responsive to INCS therapy, the addition of ipratropium bromide is beneficial. Intranasal ipratropium bromide plus intranasal beclomethasone was more effective than either active agent alone in reducing the average severity and duration of rhinorrhea in AR and NAR.[473]

INCS with intranasal decongestant

Recommendation 26. *CBS:* We suggest that patients with persistent nasal congestion unresponsive to an INCS or to an INCS/INAH combination be offered combination therapy with addition of an intranasal decongestant for up to 4 weeks.

Strength of the recommendation: Conditional

Certainty of evidence: Low

In PAR and SAR, concurrent administration of INCS and intranasal decongestants provides greater reduction in nasal congestion symptoms and greater improvement in nasal volume than that of an intranasal decongestant alone.[405,406] Furthermore, the combination tended to reduce nasal congestion faster than the INCS alone. When intranasal decongestant was given along with the intranasal steroid once a day for up to 2 weeks, the development of rhinitis medicamentosa, a concern with intranasal decongestant use as monotherapy, did not occur.[405,406] In addition, in a small study where 19 healthy subjects received intranasal decongestant for 2 weeks followed by the addition of INCS for 3 days, oxymetazoline-induced tachyphylaxis and rebound congestion were reversed by intranasal fluticasone.[474] In a 4-week, DBPC trial involving 50 patients with chronic rhinitis taking INCS and cetirizine with persistent nasal congestion, the addition of oxymetazoline provided significant reduction in nasal congestion scores compared with placebo without the development of rhinitis medicamentosa.[475] A *post hoc* analysis demonstrated that the addition of oxymetazoline afforded significantly greater nasal congestion reduction in the AR compared with in the NAR subgroup.[475] Whereas the combination of an INCS and an INAH remains the preferred and most supported option in patients with AR with persistent symptoms after monotherapy (see above), it might be reasonable to consider adding an intranasal decongestant to an intranasal steroid for the first few days of therapy in patients with AR and significant nasal congestion. At this time, existing evidence is scant and is not sufficient to support the prolonged use of the above-mentioned combination.

Oral antihistamine with oral decongestant

Recommendation 27. *CBS:* We suggest that for patients with AR and nasal congestion uncontrolled with an oral antihistamine, the clinician consider the addition of pseudoephedrine, when tolerated. (See Recommendation 18.)

Strength of recommendation: Conditional

Certainty of evidence: Moderate

Controlled studies demonstrate that combination of oral antihistamine and oral decongestant is more effective in reducing symptoms of AR, including nasal congestion, than the individual components are,[476-478] but adverse effects of oral decongestants are a concern. Given the evidence that this combination is effective, if this regimen is prescribed, the clinician should take into account the dose-response relationship of the side effect profile for oral decongestants and titrate to the lowest effective dose. As indicated in Figs 2 and 3, pharmacologic options other than an oral antihistamine with an oral decongestant (eg, INCS or INAH) generally are preferred, but the selection to use an oral antihistamine with an oral decongestant may be made in a shared decision-making discussion. As presented in the rhinitis 2008 practice parameter,[409] pseudoephedrine is far superior to other decongestants; however, there are limited antihistamine-pseudoephedrine combinations (eg, fexofenadine/pseudoephedrine). If a fixed combination is chosen, side effects such as insomnia should be taken into account. If side effects with the fixed combination are an issue for the patient, the dose should be adjusted, if possible, or the fixed combination stopped and either separate monotherapy products selected to