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# Efficacy and safety of intranasal corticosteroids approved for over-the-counter use

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## Abstract

**Background:** Allergic rhinitis (AR) is a common disorder affecting 20%-25% of Canadians.[1] Intranasal corticosteroids (INCSs) are a mainstay of AR treatment, and some are available over the counter (OTC). The aim of this review was to evaluate the efficacy and safety of INCSs approved for OTC use.

**Methods:** A search using keywords allergic rhinitis, anti-allergic agents, intranasal administration, fluticasone, and triamcinolone was conducted on Ovid MEDLINE and Google Scholar. The search was limited to placebo-controlled studies published from 1991 to present. Studies were included that evaluated the efficacy of intranasal fluticasone propionate or triamcinolone acetonide for the treatment of seasonal or perennial AR.

**Results:** Six trials met the inclusion criteria, 3 evaluating fluticasone propionate intranasal spray (FPNS)[2-4] and 3 evaluating triamcinolone acetonide intranasal spray (TANS),[5-7] vs placebo. A total of 1218 and 747 subjects were enrolled in the FPNS and TANS trials, respectively. The primary efficacy measure was reduction in nasal symptoms scores (NS). FPNS demonstrated statistically significant reduction in NS when compared with placebo ($P < .01$) and reduction in obstruction upon awakening ($P < .01$), indicating efficacy lasting 24 hours. One study evaluating reduction in ocular symptoms (OS) showed FPNS significantly reduced OS when compared with placebo ($P = .002$). TANS also demonstrated significant reduction in NS when compared with placebo ($P < .05$) across all trials. Overall, safety evaluations indicated both FPNS and TANS were well tolerated.

**Conclusions:** As more INCSs for AR become available OTC, the role of the health professional is pivotal in diagnosis, treatment selection, and education of patients with AR. The efficacy and safety of INCSs is well established. Allergic Rhinitis and its Impact on Asthma (ARIA) and Canadian guidelines recommend the use of INCSs to manage mild persistent to moderate-to-severe AR. Health professionals should feel comfortable in recommending an INCS for use in these patients.

## Background

**Allergic rhinitis: disease state and impact**

- Allergic rhinitis (AR) is a chronic inflammatory disease that affects 10%-30% of Americans[8] and 20%-25% of Canadians.[1] The prevalence of AR is increasing globally, affecting up to 40% of people worldwide[9]
- AR is clinically characterized by symptoms including nasal discharge, itching, sneezing, and nasal congestion[4]
- AR is associated with other inflammatory disorders including asthma, rhinosinusitis, and allergic conjunctivitis[10]
- The effects of AR on quality of life (QOL) are well established, with adverse effects on sleep, school, work productivity, and social life.[10] AR has been classified as a major chronic respiratory disease due to its high prevalence and impact on QOL[9]
- AR is also associated with a significant financial burden: direct medical cost in the United States increased from $6.1 billion in 2000 to $11.2 billion in 2005, greater than for diabetes, coronary heart disease, and asthma[11]

**Treatment**

- Intranasal corticosteroids (INCSs) are considered the most effective medication for management of AR symptoms and have become a mainstay of AR therapy, with an increasing number now available over the counter (OTC)[8]
- Practice guidelines and parameters have been developed to classify AR symptoms and provide treatment recommendations. In Canada, the rhinitis guidelines provide an approach to assessment of symptoms as well as treatment selection for Canadian health care providers.[12] The Canadian guidelines recommend nonsedating oral antihistamines for the relief of sneezing, pruritus, and rhinorrhea in patients with milder symptoms,[12] while INCS monotherapy or in combination with an antihistamine is recommended for moderate-to-severe intermittent symptoms or mild persistent rhinitis.[12] More recently, a global guideline, the Allergic Rhinitis and its Impact on Asthma (ARIA), was developed in collaboration with the World Health Organization.[13] The ARIA guideline provides a strong recommendation for INCSs for the treatment of AR in adults.

**Summary and objective**

- Many patients who suffer with AR seek care from specialists who are key to recognizing and assessing the symptoms of AR and recommending appropriate treatment(s) based on symptom presentation, duration, and severity, while minimizing treatment-related adverse events. Therefore, it is important for practitioners to have a good understanding of the efficacy and safety of INCSs that are available OTC
- The objective of this literature review was to summarize available published evidence for OTC INCSs in Canada

## Methods

A comprehensive literature search using keywords allergic rhinitis, anti-allergic agents, intranasal administration, fluticasone, and triamcinolone was conducted on Ovid MEDLINE and Google Scholar. The search was limited to placebo-controlled studies published from 1991 to present. Studies were included that evaluated the efficacy of fluticasone propionate intranasal spray (FPNS) or triamcinolone acetonide intranasal spray (TANS) for the treatment of seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR). In terms of treatments, the search was limited to FPNS and TANS, as these are the 2 INCSs available OTC.

## Results

Six trials met the inclusion criteria, 3 evaluating FPNS,[2-4] and 3 evaluating TANS,[5-7] vs placebo. A total of 1218 and 747 subjects were enrolled in the FPNS and TANS trials, respectively. Four trials evaluated patients with SAR (N=1,422),[2,4,5,7] and 2 trials evaluated patients with PAR (N=543).[3,6] All studies utilized OTC-recommended dosing of FPNS and TANS: FPNS was administered at a dose of 200 mcg daily, and TANS was administered at a dose of 220 mcg daily. **Table 1** summarizes the characteristics of the studies included. The primary outcome measure was reduction in nasal symptoms in all studies with the exception of one, which evaluated reduction in ocular symptoms.

**Table 1. Characteristics of the studies.**

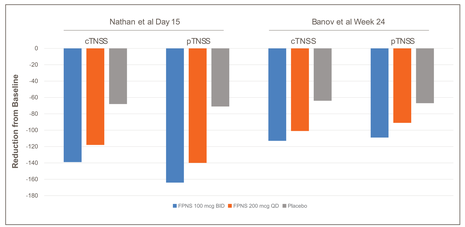
| Trial | Design | Participants | Duration of protocol (wk) | Intervention | Outcomes |
|---|---|---|---|---|---|
| **Nathan et al[2]** | M, R, DB, PC, PG | N=227; mean age across arms, 32.7-34.9 y (range, 18-62 y) with SAR | 2 | FPNS 100 mcg BID vs FPNS 200 mcg QD vs placebo NS | cTNSS, pTNSS, evaluation of response to therapy |
| **Banov et al[3]** | M, R, DB, PC, PG | N=365; mean age across arms, 35-36 y (range, 12-74 y) with PAR | 24 | FPNS 100 mcg BID vs FPNS 200 mcg QD vs placebo NS | cTNSS, pTNSS, evaluation of response to therapy |
| **Ratner et al[4]** | M, R, DB, PC, PG | N=626; mean age across arms, 40.4-40.5 y (range, 12-79 y) with SAR | 2 | FPNS 200 mcg QD vs placebo NS | rTOSS, evaluation of response to treatment |
| **Settipane et al[5]** | M, R, DB, PC, PG | N=429; mean age across arms, 37 y (range, 18-79 y) with SAR | 3 | TANS 220 mcg QD vs placebo NS | NI, evaluation of response to treatment |
| **Kobayashi et al[6]** | M, R, DB, PC, PG | N=178; mean age across arms, 30-32 (range, 11-59) with PAR | 4 | TANS 220 mcg QD vs placebo NS | NI, evaluation of response to treatment |
| **Munk et al[7]** | M, R, DB, PC, PG | N=140; mean age across arms, 35-37 (range, 20-65) with SAR | 2 | TANS 220 mcg QD vs placebo NS | NI, evaluation of response to treatment |

BID, twice daily; cTNSS, clinician-rated total nasal symptom score; DB, double-blind; FPNS, fluticasone propionate intranasal spray; M, multicenter; NI, nasal index; NS, nasal spray; PAR, perennial allergic rhinitis; PC, placebo-controlled; PG, parallel group; pTNSS, patient-rated total nasal symptom score; QD, once daily; R, randomized; rNCSS, reflective nasal congestion symptom score; rTOSS, reflective total ocular symptom score; TANS, triamcinolone acetonide intranasal spray; SAR, seasonal allergic rhinitis; y, years.

**Efficacy: Nasal Symptoms**

**Figure 1** illustrates the effects of FPNS on clinician-rated total nasal symptom score (cTNSS) and patient-rated total nasal symptom score (pTNSS) in the Nathan et al[2] and the Banov et al[3] studies.

**Figure 1. Clinician- and patient-rated reduction in total nasal symptom scores with FPNS or placebo.**




*P* < .05 for both FPNS groups vs placebo in both studies.

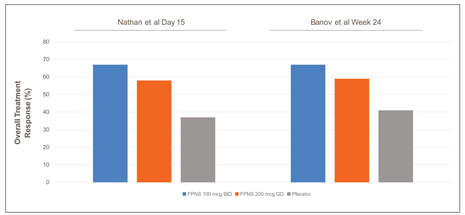
BID, twice daily; cTNSS, clinician-rated total nasal symptom score; FPNS, fluticasone propionate intranasal spray; pTNSS, patient-rated total nasal symptom score; QD, once daily.

## Results (cont'd)

In both studies, the 2 FPNS dosing regimens provided statistically significant reductions in total nasal symptom scores vs placebo (all $P < .05$).

Results of the clinician-rated overall assessment of response to treatment in the Nathan et al[2] and the Banov et al[3] studies are illustrated in **Figure 2**. More patients receiving FPNS demonstrated moderate or significant improvement in symptoms compared with patients receiving placebo ($P < .01$ for both FPNS groups vs placebo in both studies). There was no difference in response between the 2 FPNS groups in either study.

**Figure 2. Clinician-rated overall evaluation of response after treatment with FPNS or placebo (significant or moderate improvement).**



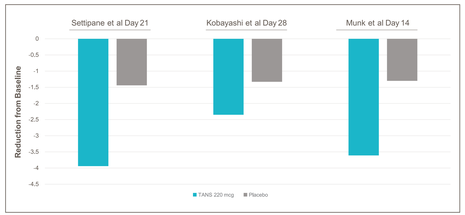

*P* < .01 for both FPNS groups vs placebo in both studies.

BID, twice daily; FPNS, fluticasone propionate intranasal spray; QD, once daily.

**Figure 3** illustrates the effects of TANS on patient-rated nasal index (NI) scores in the Settipane et al,[5] the Kobayashi et al,[6] and the Munk et al[7] studies.

In all 3 studies, TANS resulted in statistically significant improvements in NI symptoms compared with placebo.

**Figure 3. Patient-rated reduction in nasal index scores with TANS or placebo.**

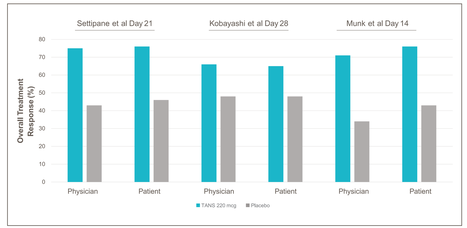



*P* < .05 for TANS vs placebo in all 3 studies.

**Figure 4** illustrates the physician- and patient-rated overall evaluation of response to treatment in the Settipane et al,[5] the Kobayashi et al,[6] and the Munk et al[7] studies. More patients receiving TANS were greatly improved or somewhat improved compared with patients receiving placebo ($P < .05$ for TANS vs placebo in all 3 studies).

## Results (cont'd)

**Figure 4. Physician- and patient-rated overall evaluation of response after treatment with TANS or placebo (greatly or somewhat improved).**



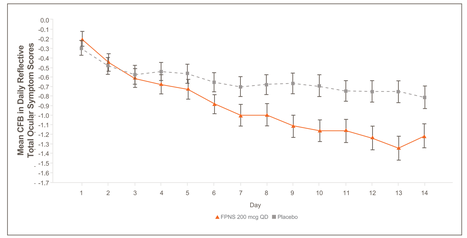

*P* < .05 for TANS vs placebo in all 3 studies.

**Efficacy: Ocular Symptoms**

One study evaluated the effect of an INCS on ocular symptoms associated with AR. Ratner et al[4] compared the effect of a 14-day course of FPNS 200 mcg once daily to placebo on ocular symptoms associated with SAR. The primary end point was mean change from baseline in patient-rated reflective total ocular symptom score (rTOSS).

**Figure 5** illustrates the mean change from baseline in patient-rated rTOSS with FPNS or placebo in the Ratner et al[4] study. The FPNS group separated from the placebo group beginning at day 4, and the magnitude of reductions increased progressively until day 14. At day 14, the least squares mean change from baseline in rTOSS was statistically greater for FPNS than for placebo ($P = .002$). Further, this difference was deemed clinically significant based on a priori criteria. In regard to individual symptoms (eye itching or burning, tearing or watering, and redness), analysis of the mean change from baseline in daily reflective symptom scores showed statistically significant differences between FPNS and placebo.

**Figure 5. Mean change from baseline in patient-rated reflective total ocular symptom score with FPNS or placebo.**




*P* = .002 for FPNS vs placebo at day 14.

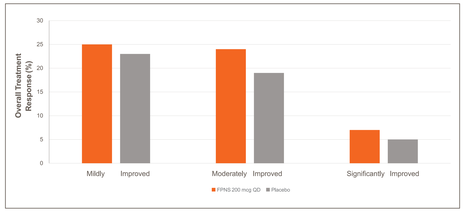
Used with permission from Ratner P, Van BJ, Mohar D, et al. *Ann Allergy Asthma Immunol.* 2015;114(2):141-147.

FPNS, fluticasone propionate intranasal spray; QD, once daily.

## Results (cont'd)

**Figure 6** illustrates the patient-rated overall evaluation of response to treatment in the Ratner et al[4] study. More patients receiving FPNS were mildly, moderately, or greatly improved compared with patients receiving placebo. The treatment difference between FPNS and placebo was statistically significant ($P = .01$).

**Figure 6. Patient-rated overall evaluation of response after treatment with FPNS or placebo.**




*P* = .01 for FPNS vs placebo.

FPNS, fluticasone propionate intranasal spray; QD, once daily.

**Safety**

Across the 6 studies, FPNS and TANS were well tolerated, with most adverse events (AEs) classified as mild or moderate in intensity. With the exception of headache, AEs consisted of local nasal events (nasal irritation, nasal burning, epistaxis) commonly associated with the application of topical nasal sprays in the presence of rhinitis. These AEs occurred at a low rate ( ~3%) and were comparable between active treatment groups and placebo groups

## Conclusions

- The results of these multicenter, randomized, placebo-controlled, double-blind studies are consistent and demonstrate that both FPNS and TANS are effective in reducing the total nasal symptoms of SAR or PAR over a 2- to 24-week period
- The onset of action is rapid, with significant improvements in nasal symptoms noted as early as 1-4 days
  - Improvements in nasal symptoms are progressive and sustained over time
- In addition to nasal symptoms, 1 study demonstrated the efficacy of FPNS in reducing ocular symptoms associated with AR
  - This is important because ocular symptoms such as itching, burning, redness, watering, and eyelid swelling are associated with AR in about 40% of patients and have documented negative effects on patients' QOL[4]
- With any OTC medication, safety is paramount. The incidence of AEs with FPNS and TANS was low, primarily local nasal events and comparable to placebo
- Specialists are key to recognizing and assessing the symptoms of AR and recommending appropriate treatment(s). INCSs are strongly recommended to relieve symptoms of AR[13], and a systematic review supports their use as first-line treatment for AR[14]
  - The availability of FPNS and TANS OTC makes them cost-effective and accessible treatment options for patients with AR
  - The data reviewed here provide strong clinical evidence to recommend use of these OTC products when appropriate

## Summary

Clinical evidence indicates that INCSs are the most effective class of medications currently available for the treatment of AR,[9,13] demonstrating superior efficacy in reducing total nasal symptom scores and nasal blockage.[12]

**References** **1.** Keith PK, Desrosiers M, Laister T, Schellenberg RR, Waserman S. The burden of allergic rhinitis (AR) in Canada: perspectives of physicians and patients. *Allergy Asthma Clin Immunol.* 2012;8(1):7. **2.** Nathan RA, Bronsky EA, Fireman P, et al. Once daily fluticasone propionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis. *Ann Allergy.* 1991;67(3):332-338. **3.** Banov CH, Woehler TR, LaForce CF, et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. *Ann Allergy.* 1994;73(3):240-246. **4.** Ratner P, Van BJ, Mohar D, et al. Efficacy of daily intranasal fluticasone propionate on ocular symptoms associated with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2015;114(2):141-147. **5.** Settipane G, Korenblat PE, Winder J, et al. Triamcinolone acetonide aqueous nasal spray in patients with seasonal ragweed allergic rhinitis: a placebo-controlled, double-blind study. *Clin Ther.* 1995;17(2):252-263. **6.** Kobayashi RH, Beaucher WN, Koepke JW, et al. Triamcinolone acetonide aqueous nasal spray for the treatment of patients with perennial allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther.* 1995;17(3):503-513. **7.** Munk ZM, LaForce C, Furst JA, Simpson B, Feiss G, Smith JA. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1996;77(4):277-281. **8.** Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol.* 2008;122(2 Suppl):S1-S84. **9.** Bousquet J. ARIA in the pharmacy: management of allergic rhinitis symptoms in the pharmacy. Allergic rhinitis and its impact on asthma. *Allergy.* 2004;59(4):373-387. **10.** Bousquet J, Van CP, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001;108(5 Suppl):S147-S334. **11.**Hay JW, Kaliner MA. Costs of second-generation antihistamines in the treatment of allergic rhinitis: US perspective. *Curr Med Res Opin.* 2009;25(6):1421-1431.**12.** Small P, Frenkiel S, Becker A. Rhinitis: A practical and comprehensive approach to assessment and therapy. *J Otolaryngol.* 2007;36(Suppl 1):S5-S27. **13.** Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol.* 2010;126(3):466-476. **14.** Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ.* 1998;317(7173):1624-1629.

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