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Patient Preference of Inhaled Nasal Corticosteroids

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Efficacy, Safety, and Patient Preference of Inhaled Nasal Corticosteroids: A Review of Pertinent Published Data

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ABSTRACT

Most clinical studies of inhaled nasal corticosteroids have established comparable safety and efficacy; therefore, there remains little to distinguish the various products from each other in the treatment of allergic rhinitis. However, patient preference is recognized increasingly as an important factor in selecting appropriate treatment. This review discusses the different methodologies that have been used to measure patient preference for intranasal corticosteroids. Patient questionnaires and other instruments for assessment that are used to measure such preferences are discussed as well as several different study designs. Now, the challenge is to implement more studies that show the reliability and consistency of instruments used to assess patient preference.
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Physicians have a choice of several intranasal corticosteroids to prescribe for patients with allergic rhinitis. Although there have been countless contributions to the literature reviewing the safety and efficacy of these products, the issue of patient preference has been discussed relatively sparingly. As Taylor[1] concluded, in an article on understanding patients' choices, patient preferences are an integral part of the practice of medicine; therefore, because patients are becoming increasingly involved with their own health care, it has become more important to understand how these preferences are generated and how they may influence a patient's effective participation in the health care decisions that are being made jointly with the physician.

Most studies have indicated that there is little to distinguish the different commercially available intranasal steroids regarding their safety and efficacy when they are used in their recommended dosages. However, physicians have noted that many times patients do have preferences and they often do not hesitate to express them. Most of the time, the reasons for these preferences are determined by a number of product attributes including its overall acceptability, delivery device, sensory attributes, and price. This article discusses some of the studies that have attempted to delineate the factors surrounding such patient preferences.

COMPARATIVE EFFICACY OF INHALED NASAL CORTICOSTEROIDS

In most studies of intranasal steroid efficacy, a symptom scale is used to assess performance. In addition, a quality-of-life tool is sometimes incorporated. Two recent clinical trials compared the efficacy of various intranasal corticosteroids in more than 900 patients. Mandl *et al.*[2] compared once-daily administration of mometasone furoate with fluticasone propionate for the treatment of perennial allergic rhinitis and Malone *et al.*[3] compared fluticasone with triamcinolone acetonide aqueous in patients with seasonal allergic rhinitis.

The first study, a 12-week, randomized, double-blind, double-dummy parallel group study of 550 patients (aged 12–77 years) with perennial allergic rhinitis,[2] assessed efficacy using a 4-point scale (0 = absent to 3 = severe) for

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rhinorrhea, congestion, sneezing, itching, burning, tearing, redness, and ear/palate itch. There were three treatment arms: (1) 200 μg of mometasone furoate with fluticasone propionate placebo, (2) 200 μg of fluticasone propionate with mometasone furoate placebo, and (3) mometasone furoate placebo with fluticasone propionate placebo. Each was administered in a dosage of 2 sprays per nostril once daily in the morning. Both fluticasone and mometasone caused significant reductions in mean daily reflective total nasal symptom score (TNSS; the sum of individual NSS, *i.e.*, rhinorrhea, congestion, sneezing, and itch) as compared with placebo, with no significant differences between each other at any time period. Both active treatments also numerically (but not statistically) reduced the nonnasal symptoms (*i.e.*, itch/burning, tearing, redness, and ear/palate itch). Regarding safety, there were no differences in tolerability between treatment groups. The authors concluded that fluticasone and mometasone are equally efficacious and well tolerated in patients with perennial allergic rhinitis.

In the second study, a multicenter, randomized, parallel-group, single-blind study,[3] 352 patients with seasonal allergic rhinitis were randomized to receive 2 sprays in each nostril of 220 μg of triamcinolone acetonide aqueous or 200 μg of fluticasone propionate once daily in the morning for 3 weeks. Efficacy was assessed using a similar 4-point scale (0 = absent to 3 = severe) for nasal discharge, nasal stuffiness, nasal itching, sneezing, ocular itchiness, tears, and redness. In addition, a Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[4] was used to assess patient quality of life at baseline and end of treatment. Adverse experiences were collected on diary cards at baseline and week 3. The results showed that fluticasone and triamcinolone both provided comparable improvement in total nasal and eye symptoms in patients with seasonal allergic rhinitis. Quality of life, as defined by the overall RQLQ, also was improved significantly by both treatments, with no significant difference at the end of treatment. The occurrence of adverse events was similar in both groups.

These two studies, which are just a sample of many in the literature, lead to the conclusion that differences in efficacy between the intranasal steroids are difficult to detect.

COMPARATIVE SAFETY OF INHALED NASAL CORTICOSTEROIDS

A similar picture is portrayed by reviewing the safety studies of modern intranasal steroids in the literature. For example, Wilson *et al.*[5] examined the effects of various intranasal corticosteroids on adrenal, bone, and white blood cell markers in patients with allergic rhinitis. In a single-blind, randomized, four-way crossover study of 20 patients, 24-hour plasma cortisol and urine cortisol/creatinine measurements were taken from serial blood and urine samples after 5 days of treatment at steady state with a 7-day washout interval. Three nasal corticosteroids (200 μg of budesonide, 200 μg of mometasone furoate, and 220 μg of triamcinolone acetonide aqueous) and placebo were administered once daily. There was no significant difference between placebo and the active treatments in any of the markers of adrenal suppression; the diurnal circadian rhythm was unaffected and there were only a few patients with abnormally low cortisol values. Regarding the bone and white blood cell markers, the active treatments produced no significant suppression of osteocalcin or the blood eosinophil count compared with placebo. These results reflected the good safety profile of these aqueous intranasal corticosteroid preparations when they are used at clinically recommended dosages.

In another study, Skoner *et al.*[6] evaluated the effect of triamcinolone acetonide aqueous and fluticasone propionate nasal sprays on hypothalamic-pituitary-adrenal (HPA) axis function and short-term growth in 59 4- to 10-year-old children with allergic rhinitis. In this double- or single-blind, placebo-controlled, four-way crossover study, patients were randomized to receive 110 μg of triamcinolone (2 sprays), 220 μg of triamcinolone (4 sprays), 200 μg of fluticasone (4 sprays), or placebo (2 or 4 sprays). After a 2-week baseline period, patients were evaluated weekly for four 2-week treatment periods (and three 2-week intervals between treatment periods). There were no clinically significant short-term effects on linear lower-leg growth rate after either once-daily triamcinolone or fluticasone when administered at recommended doses. One hundred ten or 220 μg of triamcinolone once daily did not suppress HPA axis function; however, 200 μg of fluticasone once daily for the same duration significantly suppressed HPA axis function. These results suggest there may be important differences in adrenal effects among intranasal corticosteroids.

In a long-term growth study, Agertoft and Pederson[7] examined the effect of inhaled budesonide on adult height in children with asthma. This prospective studied reported on 211 children who attained adult height: 142 budesonide-treated children with asthma, 18 control patients with asthma who never received inhaled corticosteroids, and 51 healthy siblings of patients in the budesonide group who also served as controls.

The 10-year growth data for children who reached adult height showed that although budesonide was associated with a significant change in growth rate during the first years of treatment, as compared with the run-in period, the adult height was not affected adversely. The initial growth retardation was significantly correlated with age ($p = 0.04$), with a more pronounced reduction in younger children. Furthermore, the budesonide-treated children, 40 of whom also used intranasal steroids for an average of 24 months, reached their targeted adult height to the same extent as their healthy siblings and the children in the control group.[7]

These studies did not include instruments to assess patient preferences. However, patient preference tools could become a routine part of these types of clinical studies.

COMPARATIVE DATA ON PATIENT PREFERENCE OF INHALED NASAL CORTICOSTEROIDS

A review of the literature reveals several studies that more specifically analyzed the differences in intranasal corticosteroids with respect to patient preference. In the first study, Adamopoulos *et al.*[8] compared the efficacy and acceptability of budesonide (200 μg twice daily [b.i.d.]) and beclomethasone dipropionate (100 μg four times daily [q.i.d.]) in adults with perennial allergic rhinitis. This clinical trial used an open, randomized, crossover design. There were 6 weeks of treatment with each drug, with patient visits every 3 weeks. Scores for blocked nose, runny nose, sneezing, and eye symptoms were recorded on daily diary cards. Efficacy was assessed using a 0–3 scale in which 0 = no symptoms and 3 = severe symptoms (*i.e.*, sufficiently troublesome to interfere with normal daily activity or nighttime sleep). With regard to the efficacy results, the mean TNSS was significantly ($p = 0.001$) lower with budesonide than with beclomethasone. Also, there were significantly fewer reports of blocked nose ($p = 0.004$), runny nose ($p = 0.0005$), and sore eyes ($p = 0.047$) during budesonide treatment as compared with beclomethasone treatment.

A fairly simple assessment of patient preference was performed also; preference for "effects," "side effects," and "overall" was stated by the patient at the end of the study. A significantly greater proportion of patients stated a preference for budesonide over beclomethasone based on effect ($p = 0.0001$), side effects ($p = 0.01$), and overall ($p = 0.0001$). The instrument used here to address patient preference is perhaps one of the first seen. It shows that assessment of preference can be built into what is essentially a traditional comparative trial of safety and efficacy.

Grubbe *et al.*[9] performed a study in patients with perennial allergic rhinitis in which intranasal therapy with triamcinolone acetonide aerosol (220 μg once daily) was compared with beclomethasone dipropionate (168 μg b.i.d.). This study was especially interesting in that it compared patient preferences for an aerosol preparation (triamcinolone) versus an aqueous preparation (beclomethasone). The 4-week, single-blind, randomized, controlled, multicenter, parallel-group trial was designed to compare the efficacy, tolerability, and specific treatment-related side effects in 313 patients. Patients recorded symptoms (rhinorrhea, nasal congestion, sneezing, nasal itching, and postnasal drip) in daily diaries. Symptom reduction also was assessed by physicians on a 5-point scale (0 = no relief to 4 = complete relief) every 2 weeks. To assess specific treatment-related side effects from the study medications, patients completed a daily questionnaire in which they recorded the occurrence of 10 specific complaints known to be associated with intranasal steroids (Table I). If patients responded with a "yes" to a complaint, they rated the annoyance of that complaint on a scale of 0–5. The results of this trial indicated that triamcinolone acetonide aerosol is comparable with beclomethasone dipropionate in relieving the nasal symptoms of perennial allergic rhinitis. Both treatments were well tolerated, although specific treatment-related events occurred significantly more frequently and were significantly more severe with beclomethasone. Occurrence of medication run-off was less with triamcinolone than with beclomethasone ($p = 0.001$); severity of medication run-off also was less with triamcinolone ($p = 0.0024$). Bad taste was more severe in the patients who received beclomethasone ($p = 0.0024$).

TABLE I

Daily Patient Questionnaire on Treatment-Related Side Effects[9]

1. Some of the medicine ran down my throat
2. Some of the medicine ran out my nose
3. The medicine tasted bad, left a bad taste
4. It made me sneeze
5. It made my throat sore
6. It made my nose sting and/or burn
7. It made my nose bleed
8. It dried the inside of my nostrils
9. There was blood in my nasal mucus when I blew my nose
10. It made my nose feel stuffed up

Response was either yes or no. If yes, then attributes were rated on a scale of 0–5.

An even more sophisticated assessment of patient preferences for intranasal steroids was undertaken in a study by Gerson *et al.*,[10] who determined the preference of adults with allergic rhinitis for triamcinolone acetonide aqueous, fluticasone propionate, or beclomethasone dipropionate based on sensory perceptions and acceptability. In this double-blind crossover study of 94 patients, preference was assessed using a 13-point questionnaire, which was administered by a blinded third-party interviewer after each drug treatment. The actual treatment procedure consisted of 2 sprays/nostril, in random order, of each study drug. Before each treatment, patients neutralized the senses by chewing unsalted crackers, rinsing the mouth with room temperature water, and sniffing a swatch of wool cloth. Treatments occurred at 30-minute intervals. Immediately after each treatment, 10 items from the questionnaire were asked by the interviewer; 2 minutes after each treatment, the three remaining items were asked (Table II).

The order of drug administration did not affect mean ratings for each product. However, "initial irritation" scores were significantly higher when treatments were administered in the order of fluticasone–triamcinolone–beclomethasone, and "liking of taste" scores were significantly lower when treatments were administered in the order of beclomethasone–fluticasone–triamcinolone.

The patient preference instrument in this study used a 100-point scale to assess each attribute, which should enable

TABLE II

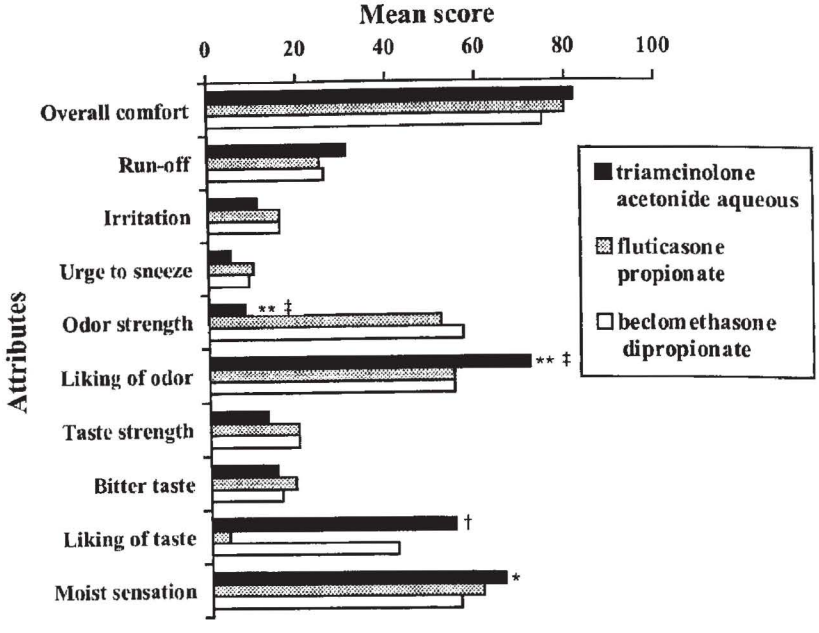
Nasal Spray Evaluation Questionnaire[10]

Item	Scale	
	Score = 0	Score = 100
Immediately after Administration		
Overall comfort	Not at all comfortable	Extremely comfortable
Run-off	None at all	An extreme amount
Irritation	None at all	An extreme amount
Urge to sneeze	No urge at all	Extremely strong urge
Odor strength	No odor at all	Extremely strong odor
Liking of odor	Dislike an extreme amount	Like an extreme amount
Taste strength	No taste at all	Extremely strong taste
Bitter taste	Not at all bitter	Extremely bitter
Liking of taste	Dislike an extreme amount	Like an extreme amount
Moist sensation	Extremely dry	Extremely moist
2 Minutes after Administration		
Run-off	None at all	An extreme amount
Irritation	None at all	An extreme amount
Overall liking of product	Dislike an extreme amount	Like an extreme amount

a more sensitive assessment of product differences. There was a significant preference for triamcinolone over fluticasone for "liking of odor," "liking of taste," "odor strength," and "overall liking of product." Patients also significantly preferred triamcinolone over beclomethasone for "liking of odor," "moist sensation," and "odor strength" (Figs. 1 and 2).

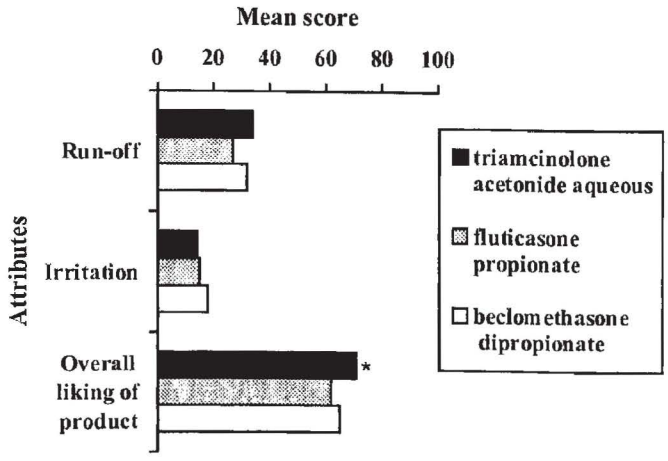
This study shows that patients are able to distinguish one medication from another. In addition, performing an assessment both immediately after administration as well as 2 minutes thereafter offers a more realistic evaluation of a patient's preference because it more accurately follows formation of preference in real life.

This instrument for assessing patient preference was adapted and then used in a study by Bachert *et al.*[11] They assessed the same 10 items as Gerson *et al.*[10] immediately after administration of each product; however, they included an additional item (strength of aftertaste) for assessment 2 minutes after administration.



Triamcinolone is significantly better than beclomethasone; $^{*}P \leq .01$, $^{**}P \leq .001$.
Triamcinolone is significantly better than fluticasone; $^{\dagger}P \leq .04$, $^{\ddagger}P \leq .001$.

Figure 1. Results immediately after administration.[10]



Triamcinolone is significantly better than FP; *$P \leq .05$.

Figure 2. *Results 2 minutes after administration* (N = 94).[10]

In this double-blind crossover study with 95 patients, triamcinolone acetonide aqueous (55 μg/spray), fluticasone propionate (50 μg/spray), and mometasone furoate (50 μg/spray) were compared for patient preference in adults with allergic rhinitis. Within 7 days of a screening visit, preference was assessed with the Nasal Spray Evaluation Questionnaire administered by a blinded third-party interviewer after treatment. The three treatments (2 sprays/nostril daily) were administered in random order at 30-minute intervals. As with the previous study design, patients neutralized their senses (with unsalted crackers, mouth rinse, and swatch of wool cloth) before each treatment.

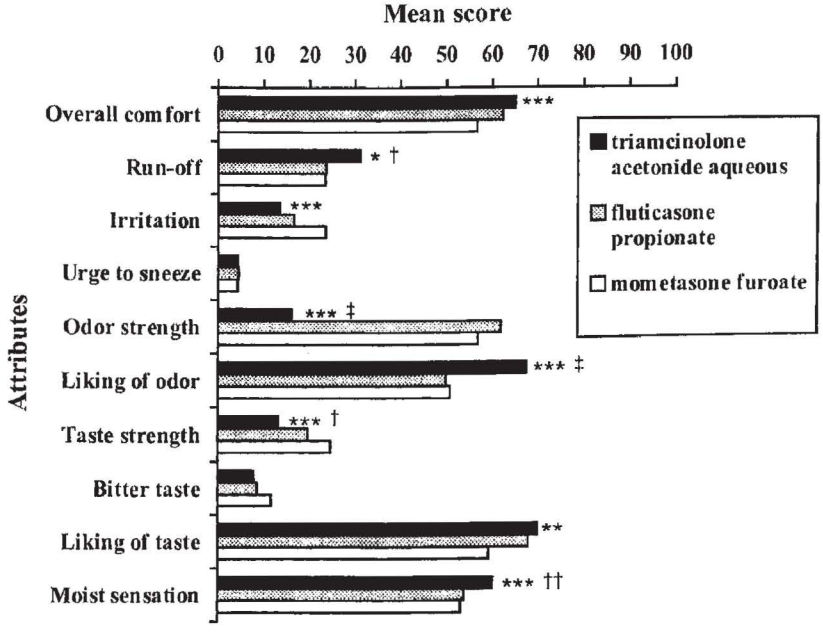
Immediately after administration, patients showed a significant preference for triamcinolone over fluticasone for liking of odor, odor strength, moist sensation, and strength of aftertaste and 2 minutes after administration, they significantly preferred it for strength of aftertaste, amount of irritation, and overall liking of the product. Patients significantly rated triamcinolone over mometasone for overall comfort, odor strength, liking of odor, taste strength, liking of taste, moist sensation, and irritation immediately after administration and for strength of aftertaste, amount of irritation, and overall liking of the product 2 minutes after administration (Figs. 3 and 4).

TABLE III

Overall Nasal Spray Questionnaire[11]

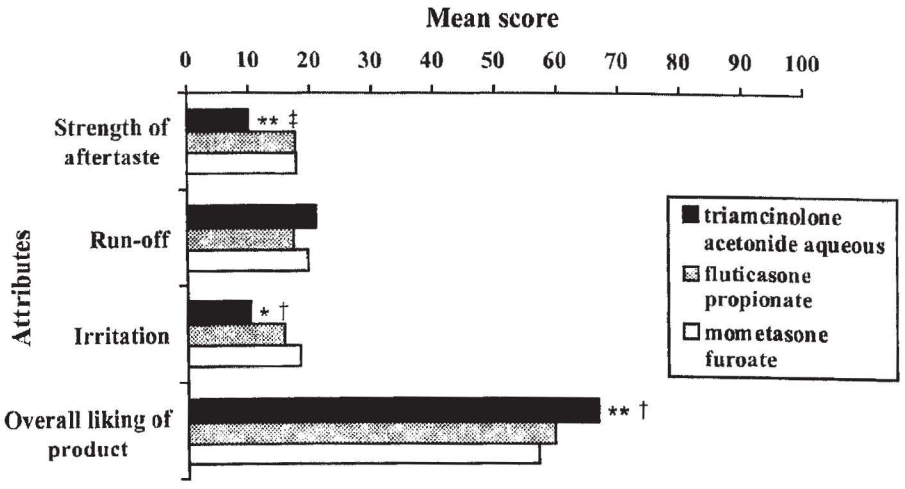
1. Rank your preference for the prescription of each nasal spray as 1 (preferred to be most prescribed) to 3 (preferred to be least prescribed)
2. Evaluate your expected compliance for each nasal spray on a scale of 1 (definitely comply with the prescription) to 4 (definitely not comply with the prescription)

This study also addressed the issue of compliance and preference by including two additional questions to the patients, which they answered after all three treatments had been administered (Table III). Overall, 54.7% of patients would prefer to be prescribed triamcinolone as opposed to those who would prefer fluticasone (21.1%) and mometasone (24.2%; $p = 0.001$). The majority of patients (67.4%) responded that they definitely would comply with triamcinolone therapy compared with 54.7% who responded that they would comply with fluticasone and 49.5% who would comply with mometasone.



TAA is significantly better than MF; *P ≤ .05, **P ≤ .01, ***P ≤ .001.
TAA is significantly better than FP; †P ≤ .05, ††P ≤ .01, ‡P ≤ .001.

Figure 3. *Results immediately after administration* (N = 95), *intent to treat.*[11]



TAA is significantly better than MF; $^{*}P \leq 0.01$, $^{**}P \leq 0.001$.
TAA is significantly better than FP: $^{\dagger}P \leq 0.05$. $^{\ddagger}P \leq 0.01$.

Figure 4. Results 2 minutes after administration (N = 95), *intent to treat.*[11]

PATIENT PREFERENCE QUESTIONNAIRES AND INSTRUMENTS: CONCLUSIONS

Based on the data discussed in this review, it can be concluded that published data on patient preference for intranasal steroids tend to support our experience in practice. In the studies reviewed, patients were able to discriminate among intranasal corticosteroids based on each product's sensory attributes. However, it is clear that no standard patient preference questionnaire is available at this time. In fact, there is only one patient preference questionnaire that has been used in more than one study in the same format.[10,11] Now, the challenge is to develop a reliable, consistent instrument and method of assessment for these patient preference studies, which will allow us to include patient preference as a standard assessment tool in all of our intranasal steroid clinical studies. Some of the questions yet to be explored further are as follows:

- Method of assessment—can this be accomplished adequately by the patient or should it be administered by a third party?
- Rating scale—should the optimum range be 0–4, 0–100, or something else?
- Study design—is a crossover design better than a parallel group? What should the duration of drug therapy be (*i.e.*, is a single-dose study superior to one that examines the effects of chronic treatment)? Also, is an immediate assessment more important than a 2-minute assessment (or *vice versa*?)
- What is the optimum patient sample size?
- When can differences in the results be recognized as being clinically significant?

Meanwhile, as these questions are being addressed in clinical studies, we as physicians can incorporate patient preference into everyday interaction with patients in our practices.

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